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ANNALS OF INTERNAL MEDICINE

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ANNALS OF INTERNAL MEDICINE

OFFICIAL PERIODICAL OF THE AMERICAN COLLEGE OF PHYSICIANS

DEPARTMENT OF REVIEWS

The Journal will make an especial feature of the reviews of monographs and books bearing upon the field of Internal Medicine. Authors and publishers wishing to subject such material for the purposes of review should send it to the editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all matter sent will be made in the department of reviews.

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*Deceased

Address*

By Dr. George E. Vincent
President of the Rockefeller Foundation, New York

MR. Toastmaster, Ladies and Gentlemen: I have been in town all day, but this is the first session of this gathering which I have attended. I offer no apology, but I do vouchsafe an explanation. I have had so much to do as a layman with medical meetings that I have stopped going to them entirely. I have so little immunity against suggestion of symptoms that I dill not expose myself to this sort of thing any longer.

The last medical meeting I attended was a meeting of the New York Academy of Medicine, which was devoting two weeks to the study of old age. They called it gerontology, but it was the same old thing. They asked me to make an address at this opening gathering. I prepared one of those affable, urbane and slightly cheerful views of old age which I hoped to present with something like optimism. I did my best. I did not say too much about old age. I did not try to gloss the thing over unduly. I had to admit that old age had its disadvantages, but I expressed in a timid, tentative, modest way the hope that society might find some slight use for people who are over seventy years of age. Then I made a great mistake. Having made my address, I didn't go away; I stayed and I listened to one of the most diabolically accurate and scientific pathologists that this world has ever produced. He spoke for an hour and a quarter. He spoke about old age with a definiteness, with a cold-bloodedness that was absolutely unendurable; worse than that, he displayed before the whole company what might be called a time-table of senility. All the symptoms were shown appearing at a certain age. I had every one of them coming at precisely the scheduled time. Then he went on giving detailed, pathological, imaginative, descriptions of old age, and his general conclusion was that he couldn't for the life of him see why anybody with common sense and who wasn't already the victim of softening of the brain should want to be a victim of old age. He thought some people might possibly go on to seventy, but why anybody wanted to go on longer than that he could not himself imagine.

I haven't gotten over that yet. It was a gloomy and depressing evening, and, therefore, I resolved that I would subject myself to nothing of that kind tonight. I looked over your program and it was full of the most damaging

*Delivered at the Annual Banquet of the American College of Physicians, April 11, 1929, Boston, Mass.

and dangerous possibilities. I am glad to say that I haven't heard a single word that any of you had to contribute on any of these subjects, and I do not propose to read any of the papers if they are published. (Laughter)

I have been introduced as a doctor, but I want it distinctly understood that I do not vent myself as a doctor. A long time ago I got the degree of Doctor of Philosophy. I did not parade it. I wouldn't go so far as to say that I am ashamed of it, but at the same time when I associate with doctors of medicine, I realize the patronizing superiority with which they look down upon me and I am increasingly willing to be called "Mister," or even "George E. Vincent." (Laughter) But I got that degree of Doctor of Philosophy a long time ago, because then I was by way of being what was called a sociologist. I no longer acknowledge being a sociologist, but I still have a certain hankering after sociology. I have a sort of wistful, backward look at my sociological days, and when I see gathered before me a co-educational company of this kind, it brings back the old days of my professorship. It seems as though this were one magnified classroom and I find that my—and that is one of the signs of senility which appeared on the chart to which I have just referred—inhibitions are weakened and that old habits reassert themselves and that gerontism of a certain kind takes possession and will have its way. Therefore, I propose this evening, in order to put myself in some degree on an equality with you, although I have listened to none of your technical addresses, to make a sociological address. You might as well know it at the outset. If you have come to the city of Boston with the idea that you are going to enjoy yourselves in any purely frivolous way and not make appropriate sacrifices to what is sometimes courteously called the intellectual life, you are greatly mistaken. You have either got to exert your higher hemispheres or, what you have so frequently done, give the external signs of that kind of inner activity.

I want to present to you a sociological theory, though I realize that it has certain disadvantages. My children urged me never to use slang. They say it dates you so. So my sociological theories date me dreadfully. I have no doubt these sociological theories have long since been abandoned. I am sensible enough not to refer to Herbert Spencer. I know that no one thinks of him except as a delightful archeological speciment of a perfectly dessicated form of thought which no longer plays any part in the world except possibly south of the Mason and Dixon Line where it still serves the purpose of holding up a dreadful example of what atheism combined with intellectual achievements may do in the way of destroying human character and menacing the very existence of society. (Laughter) But I do revert to a theory which you will see a little later on is not wholly unrelated to the interests represented here tonight, to the theory of a French sociologist, Gabriel Tarde. In the days to which I refer, people were always trying to find some criterion of the essence of sociology. You got on very well with physics and chemistry. Then you

came to biology, and in trying to explain the differential you used *"vital."* Of course it begged the question, but it was useful, and, therefore, in biology you deal with vital phenomenon and later on philosophically discuss what you mean by vital, but at any rate it is something. When you go on from the biological into the psychological field, you bring in consciousness, although I believe Watson has ruled out consciousness. You see how far behind the times I am. Then when you come to the sociological you also have to have some sort of differentiation. What is the differentiation? Well, there was Professor Giddings who said it was consciousness of kind, and there were other people who said it was contact. That was before the advertising men made the term a household word.

There were others who thought it was a contractual relationship, but Gabriel Tarde said the essence of social relationship is imitation. He developed a most beautiful theory which he expressed in graphic terms with a picturesqueness which took the imagination. "Society," said Gabriel Tarde, "is like a vast plain and rising in this vast plain are certain mountains, and on the summit of these mountains are gorgeous individuals and groups, held up into the sunlight so that they can be seen of all the people in the plain."

These heights are the models from which imitation is spread through the masses down into the plains. Every society has its glorified heroes; every society has its élites, and it is these heroes and élites that to a very large extent determine the very nature of society and control its activities,—a very interesting theory when you come to think about it. You have no social organization unless there are, raised above the levels of the great masses of the people, these glorious mountain peaks for imitation. These are the models, says Tarde, and by imitation these models spread from individual to individual until they influence all the group; and of course with present day communication (Tarde's theory was propounded before we had the radio), the rapidity with which these marvels are spread from sea to sea and from continent to continent is simply the amazing phenomenon of our times. But it is a very interesting theory, this theory that after all a large part of society itself is constituted of centers which are imitated and that the great essential social process is the process by which necessary mountains are raised and the process by which imitation flows from them to the control, influence and management of great masses of people.

Let us examine it for a moment. What do we mean? Of course every society makes its heroes. These heroes are shining examples. These heroes have the greatest influence. These heroes are held up; they are concrete examples of the things which the group prizes, the things which the group admires, the things which the group imitates. Of course society makes its heroes, so to speak, to order. Under given conditions it has one kind of heroes; change the conditions and another sort of heroes are immediately demanded. Some of you can remember the Spanish American War—some of the men. (Laughter) The Spanish American War, of course, compared

with recent conflicts was rather a pitiful affair, but as the Irishman said, it is better than no war at all, and it is a war with respect to which we came out very handsomely. To be sure, most of our sacrifices were due to typhoid fever and other communicable diseases in our camps, but we got a few men to the front, and they were comparatively safe when we got them there. But we had heroes. We created military and naval heroes. Of course they were rather perishable; they are a perishable lot. We gave an allowance to one and kissed another, and they rapidly disappeared. (Laughter) For the time being they were exalted, they were, as Tarde would say, on the mountain peaks, and you can imagine how we were influenced, how we adults were influenced, how our boys and girls were influenced by these glorious if transitory instances of models of heroic conduct and personality set up before us.

I think if we will go on to examine things a little more carefully we will discover that after all the heroes are in an exalted manner typical of groups and that in reality the one enduring social force is not the individual but the small group of which that individual is an outstanding and conspicuous example.

Lindbergh, of course, is a great hero. Thank God up to the present time he hasn't recommended a thing for the purchase of the American people, and that, now, is the sign of true greatness. He represents in a supreme way that exalted group who represent averages. It is the group, after all, from which the hero gets his meaning. It is the group into which the hero sooner or later is merged; it is the hero who temporarily gives distinction and prestige to his group.

Therefore, the thesis that I want to propound a little while tonight is that it is the élite that determines to a very large extent the progress, the course of modern society. The élite, the small selected group, has immense influence in social organization, immense influence in social conduct, immense influence in that thing which we are not perfectly certain is true, but which for preambulatory purposes we describe as the progress of society.

The élite is a very interesting idea. Of course it is unpopular in a democracy, and what I want to talk about tonight is the élite in a democracy. The élite in a demoncracy is resented. The very idea of the élite seems to be contrary to the underlying conception of democracy, which is that everybody is just as good as everybody else. That, of course, is an entire misconception of democracy, but most of our conceptions about ourselves are entire misconceptions, and, therefore, we have contrasted frankly, and let us admit it at the outset, the idea of the élite with the idea of the many. The few competent are always an insult to the incompetent many, and the incompetent many at the same time that they grudgingly admire and follow the élite, when the fact that it is the élite is pointed out to them, are universally resentful.

It is one of the most interesting things to observe that we despise and abuse and attack the things that are essential and that we sneakingly admire. This applies to the élite known

as society. Of course it is a little difficult now to be quite sure just where this is. In the good old days that I can remember, we had a 400 in New York, and it was a great comfort to have a 400. You knew then when you were in, and most generally when you were out. There was something distinctive, there was something satisfactory, there was something definite, and when Mrs. Vanderbilt was in charge, it was very definitely known who could get in and who couldn't get in. Those were the good old days of the 400, and Ward McAllister and Mrs. Vanderbilt and the great balls that settled who was who and who wasn't.

That was a very definite sort of thing, but now all things have changed. You can't be perfectly certain, and yet in a way if you are on the inside, you know a great deal more than you do if you are on the outside.

In a very definite way there is a society. There is an inner circle, then another circle, then another circle and then still another. And the people who are in the very inner circle know very well where that leaves off and the other one begins. It is only the people outside altogether who think it is very easy to get in. Moreover, there is always the resentment. Whenever you hear a woman say that she wouldn't go if she could, if you know anything about psychology, you know then that the group exists, and exists very definitely. (Laughter)

Democracy resents the very idea of this exclusiveness, for exclusiveness is one of the characteristics of the élite. The definition of the élite is the selection of the few from the many, and you can't select the few from the many without leaving most of the many outside. That is precisely what happens. It happens in all sorts of ways. It happens in social clubs. There are clubs continually being formed. They are usually organized by the people who can't get into the other clubs, and it is a very good procedure. If you can't get into an existing élite, start one of your own, and after a while there will be people who actually feel excluded from yours, and then you know that you have begun to get an élite. It is a process that in a democracy can go on; it has its disadvantages because there is a limit to the amount of glory that can be shed upon the rapidly multiplying élites. The game is all spoiled because there are a few of the older élites that still go on behind that kind of élite, and you can't quite imitate them. Your own élite is not quite as good, it is not exactly a substitute, but it is the best you can get under the circumstances.

I remember very distinctly that this sense of being excluded is one of the very interesting characteristics of the idea of élite. I was ranging once, when I was an undergraduate, through a library. To say frankly I got in by mistake. I thought it was a popular library where novels were circulated, and instead of that, I got into the university library. I was so interested to see what it was like, now that I was there, that I looked about and I was allowed to wander. I don't know how I got in, but they let me wander about; I found books of various kinds and I got interested in them.

It is a habit. I went afterwards, but I was regarded as eccentric by my classmates, and I concealed the fact that I knew very much about the library. I did find a lot of very amusing and entertaining books. One of them was a little bit of a volume published in 1842. I took that out and found that it was written by an eccentric American who had traveled about the world a great deal. He was a graduate of Yale. He had all his honors on the front page, on the little title page, and here in the middle of this title page was this: "Blackballed at the London Athenaeum Club, 1839." (Laughter) For a while I pondered; I didn't quite know what the Athenaeum Club was, but don't you see the idea? The very fact that he had been considered for the Athenaeum Club was in itself a distinction. I don't suppose in his time there was another American that had even been put up at the London Athenaeum, and he naturally strutted about because he had at least been considered.

This matter of exclusiveness is a very interesting thing. There is a Harvard man I know who says of the Yale Club in New York, which is on Vanderbilt Avenue and 44th Street, "Membership in the Yale Club confers all the unique distinction of being a member of the Grand Central Terminal." That wasn't quite kind, because it approaches in a way to accuracy. That is a club which could not be described as intolerantly exclusive. It needs the money for one thing, and it is a Yale Club for another, and Yale represents, as you probably know, even under the shadow of Cambridge, an American democracy which is one of the most valuable, et cetera, et cetera. (Laughter)

What is the essential characterstic of an élite that is a real élite? It has prestige. Prestige is the important thing if it is going to be a real élite and if it is going to function as an élite. It is a rather curious, entertaining, and a little disconcerting thing to examine the etymology of prestige. It has the same root as that of prestidigitator, and it means illusion, deceit, trickery, wonder, amazement, fascination. Therefore, prestige of the individual is an illusion about one's own importance which gradually is translated into a reputation. You see other people taking that illusion as a reality, until finally prestige has become identical with reputation, and better than that, with a glorious reputation which confers honor and distinction.

Isn't it amusing what happens to language when you let it go? So the prestige of an élite is that the bunkum of the past has become the illustrious, characteristic, outstanding and shining distinction of the present. But we need not quarrel with the word; we know what prestige means. Prestige means that belonging to the group confers upon the individual who is a member of it a certain reputation, a certain standing, a certain distinction. What is distinction? Just something that that labels you a little and gets you out of the great common herd and mass of mankind. Everybody wants to be a little distinguished. There is nothing so bad as to be told that you are a completely average person. You are perfectly willing to admit that you are average because you want people to deny it, but you

dislike being told that you are average people. You know you are not. The whole object of your organization would be defeated if you were. You are not average people. You are extraordinary people. You are unusual people. You admit it. You take pride in it. You are doing your best to make other people envious of you, and you are gradually gaining prestige, which is what you are after. (Laughter) That is, you hope that in time the public will take you at your own valuation.

So our élites are characterized by prestige. Where do they get prestige? How can you go about acquiring prestige? It is rather interesting to analyze that a little. There is nothing better than antiquity. It seems irrational, it seems unfortunate, but if your élite is old enough, if it stretches back over generations, better if it stretches back over centuries, it becomes sacrosanct by the mere passage of time. It is one of the most irritating, one of the most annoying, one of the most utterly unendurable things that it is a real prestige and there is no getting away from it. One of the most delightful things is to suppose that by denying things, you can change the facts. You can't. The scientifically-minded person simply examines them. He may not like them, but he tries to face things as they are, and one of the most important forms of prestige is historic tradition. We laugh about the first families of Virginia. Why? Because we don't belong to them.

We make flippant allusions to Beacon Street and old Boston families, and how glad we would be if we could claim even the most distant cousinly relations to them. They have real distinction, they have real prestige, and it is a prestige that has come down through the years and it exists; it may be irrational, it may be utterly without foundation, we may be in our splendid characters, in our marvelous intellects, in all the noble qualities which we possess in such copious degree, we may be the superiors of all these people, but the public doesn't know it. That is the important thing. Prestige is something that exists in the minds of other people, and if it is there, it's there, and nothing you can say about it will change it; it's there.

So there is a prestige of antiquity. Wouldn't you like to be a member of the Royal Society of Great Britain which was founded in 1660, and which has had associated with it a list of most brilliant names in the sciences ever since that time? To be a member of the Royal Society confers real prestige, historic prestige, and it is something that people covet and prize as a possession, and it is something which has the admiration not only of the British public but of people who know what reputation in science is the world over. It is an actuality, it is there, it exists and it will go on existing for generation after generation. It is very difficult to take what might be called sudden retrospective measures with regard to your family, for example. That is something that just can't be done. Therefore, the historic business takes care of itself. There is no way in which you can make your society older than it is. It was founded, I believe, in 1915, and there you are. It will take another hundred years to

make it sacrosanct, but the time will come, if you stick to it. It ought to be a joyous thing to you to think that your successors, whatever may be your humble position, will be on the mountain peak, bathed in the light of a prestige which has back of it all the sanction of antiquity.

Then there are what are called founts of honor. Royal approval and recognition are still, in spite of all the things we say about kings and queens and royalty, a sort of prestige. How many Americans take their daughters to the Court of St. James and how many would like to? Of course, I wouldn't have that sort of thing, I don't prize that kind of thing at all, you know, "I wouldn't have my daughter go; it would interrupt her education, for one thing, because she doesn't get through school and college work until the end of June, and this comes in May. No, I don't see why mothers want that sort of thing." Ha! ha! (Laughter)

Thank goodness I have never said that. I have two daughters but they didn't get to the Court of St. James, and I would be a hypocrite if I said I might not have taken a certain satisfaction if they had. Let's be honest about these things.

There is real prestige still in recognition by royalty. Look at the birthday honors. Oh, of course we know the king doesn't do it himself, no, but he is the source of prestige, he is the immediate source of prestige. Oh, yes, yes, they contribute to the campaign funds, those knights and baronets and all the like, yes, of course. Well, perhaps they do, who knows. At any rate, it carries distinction. When you meet an Englishman, are introduced to him and he is introduced by a title, of course your democratic spirit is revolted, you don't think a thing more of him because he has got a title. Don't you? Of course you do; you know you do. That is the truth. These are the facts. What is it that goes on in your mind? What do you really think? Not analytically, not reflectively, not on a high moral plane, but how do you sneakingly feel about it? That is the real thing.

Then there are institutional sources of honor. For example, our universities. Our universities give degrees; they give two kinds of degrees, degrees for work done, and degrees as an honor. They are founts of honor for us. Look at the lists of people who have degrees at commencement time. Of course sometimes it is a little embarrassing; sometimes it is a little funny. I can't help having respect for two or three rich men I know who give money to colleges and universities but who absolutely and always refuse to accept an honorary degree. Some might call it humor, some might call it modesty, some might call it good taste; it is just as you feel.

Our universities are sources of honor; they are founts of honor; they put hallmarks on people. All the members of your college have a university hallmark of some kind. You couldn't get in if you didn't have it. Self-made people need not apply. You have got to go through and be stamped by somebody. Of course oftentimes under our democratic conditions you have to explain pretty carefully who stamped you, because there are élites among universities. That is what some

of our English friends who get honorary degrees for a price don't understand. The National University at Washington, for example, which confers degrees of all kinds by mail at twenty-five dollars up or down, does not confer in the United States an enormous amount of genuine prestige but in some foreign countries where they don't go into these things, or haven't until recently, no questions being asked, the degree coming from an American institution has conferred a certain amount of very modest distinction.

We have other sources of honor. We have academies. You know we have a national academy, an Academy of Sciences in Washington and it is a distinction to belong to that. I don't suppose you know as much about that as you might, but if you did know about it, it would be something of a distinction. (Laughter)

We have, of course, the classical example of the French Academy—the forty immortals. Well, we have an academy that was started by Mr. Howells and a group of people, and a very fine group it is. The only trouble is it hasn't been going on long enough. A couple of hundred years from now it will have a great deal of prestige, undoubtedly, throughout the United States. Now it is in the process of growing its prestige and if you examine it carefully and see what good men have belonged to it, you will feel that they have made an excellent start, but at the same time we have to admit that it does not have anything like the prestige of the French Academy—the forty immortals.

Then there is the prestige of prizes. The Nobel prize confers a distinction. We don't quite know who the Nobel people are, who award the prize, but we assume that they are very capable people, and when they give the prize, at once the individual who gets it enjoys prestige and distinction.

These are illustrations. I need not bore you with more. There is institutional prestige. Then there is a kind of prestige which seems to come from a sort of public admiration such as applies in a very humble and amusing way to some of our screen stars. Of course some of them are going to suffer I think very much because a few just have looks and not voices and under the changing conditions, voices are going to count quite as much as looks, so that a combination of appearance with voice is now going to make a new selection and we will have a new élite from Hollywood.

There is a kind of pathetic élite made by the great masses of the American people who hold these heroes and heroines up until they become set apart as tinsel Olympians, who after all have a kind of prestige. They exercise an influence, they are admired, I suppose, by millions of people all over the United States in a form of spontaneous, democratic apotheosis.

When we come to examine the essence of élites, we will discover that a limitation of numbers is a very useful thing. We are going to have just so many people and when we come to that limit there is going to be a waiting list. A waiting list always adds to a club's prestige. Sometimes they make the waiting list just on purpose to confer the prestige. A waiting

list is an enormous suggestion of a cue waiting to get in and kept waiting to get in. There is a certain satisfaction on the part of those who are inside to have those on the outside wait until there is a vacancy. Of course it is very fortunate for the people outside and they take a morbid interest in mortality tables as applied to those who are on the inside, but the limitation of numbers is a very important thing and you will find, I think, that certain élites which enjoy the greatest distinction are those which have a limitation of numbers.

If the idea is to raise the group to the very highest pinnacle of glory and to hold it there in the very sunlight of the utmost possible prestige, the forty immortals is a classic example. If there were a hundred immortals, they wouldn't be nearly so immortal. It is the limited number, and then every time an immortal dies, that canvassing of candidates, this man and that man, will he be chosen or will the other? It is a tremendous play of popular attention upon the prestige of the group, upon this conspicuous élite.

But there are élites that seek another thing. They seek a certain standard, a certain type, a certain ideal. They say, "We will not limit numbers but we will hold true to that standard," and let there be as many people as possible who can measure up to that standard, "so long as we hold to the standard we are not interested in limitation to any particular number." If the standard is high enough, you really have a limitation of number, because anybody who is at all familiar with statistics as applied to biology, as applied to psychological characteristics of individuals, knows that in any group there is a very small percentage of people who can be regarded as exceptional, as belonging to a high pinnacle of distinction—sometimes five per cent, and that is a pretty high percentage.

Now we will come down to your college. The application isn't going to be nearly as long as the preliminary. If I understand properly, your college is not an élite which sets a limit. There is an organization I believe that has assumed that 150 physicians would be the limit that it could reasonably expect to find in the United States. I don't know just what the standard is; it must be fairly high. There you have a limit, and I have no doubt there are people here (they would deny it very likely) who secretly cherish the ambition that when the mortality tables have done their duty there will be vacancies in that group which humble but competent people are ready to fill. Far be it from any member of this organization to be derelict in duty; he is prepared to go to the front and take his place when summoned. That is the right spirit. (Laughter)

Let us now examine very briefly the problem which you are facing. You are facing the problem, as I understand it, of setting a standard. Why are you setting the standard? What is your object? Of course your object is the public benefit. That, we take for granted. There is no selfish motive to animate you for a moment. In order that the standard may be raised for the welfare of the American people you are ready to sacrifice your friends, relatives, and other people who may have social ambitions in

the interest of the public; you are adamant. This is a noble position and I applaud it highly. You are bound to stand by and see that this standard is preserved.

What are the difficulties? The difficulties, of course, occur to you; you have thought them over better than I have, but I am talking from an outside point of view, sympathetic, interested, wishing you well.

Let me consider first of all with an a priori. I know nothing about your experiences, but as a reformed and retired sociologist I am *a priori* aware of certain speculations about human nature. There are certain internal difficulties. I have belonged to a few clubs, under very embarrassing situations, because we raised the standard after we got in, and when we had to break it to other people that they did not measure up to the standard, they raised a row. They said, "How did you get in?" All we could say was that we were on a new basis. (Laughter)

You are bound to have differences of judgment and there are always people who will feel that they have been unfairly excluded.

Then there is always the temptation, and it is a very real temptation, a kind of pleasure, of saying, "He is an awfully good fellow. Yes, of course he hasn't done very much lately and he has rather run on momentum since he was graduated, but he is a splendid fellow. At that St. Louis meeting you know he was the life of the party." (Laughter) I may say, by the way, if you are hard-put to it for festivity, I hope it won't go any further but I could suggest Hoboken, New Jersey, as a place. (Laughter)

Then of course sometimes there are people who say, "We think this thing has gone too far and we don't want to be disagreeable, but if you are not a little more lenient we will see; we have had quite a number of members feel that things are going a little far and we will see what can be done at the next meeting in the way of getting some other representatives on the selection committee," and so on. There are always those internal possibilities. There is no doubt about it, there is pressure brought to bear and it is a temptation to be a good fellow. There are people who go so far as to say that democracy is incapable of making its own élites from the inside, that the very essence of democracy is such a sloppy sort of good-natured comradeship that it is impossible to get a group up and hold it there, that it gets pulled down toward the great level of mediocrity which is such an enormous majority.

There are about 120,000 doctors in the United States, not counting some of those irregular people who give you such anxiety. About 80,000 of them belong to the American Medical Association. There is only one society that I know that is more exclusive, and that is the National Geographical Society. (Laughter) The American Medical Association, then, is the starting point. You begin to cull from the 80,000; you rule persons out on various grounds, and then you get to your organization with about 2,000. That looks to me as though you were pretty nearly approaching a limit. I don't know what your plans are, but

unless these doctors, unless the 80,000 doctors are a very extraordinary lot—and I am not sure that they are—you are getting pretty close to a safe élite out of 80,000. You might go another 500, who knows, and of course in time you will lift them to your own level.

A great deal has been accomplished. American Medical Association has done splendid service in raising the level of medical education in weeding out old and weak schools. Let us admit it. More than that, let us be grateful to the American Medical Association for what it has done in raising the general level, and you never can do very well with an élite until you have got a pretty good level to start from. When you are in Denver, Pike's Peak is very high because you start a mile high to climb it, and when you are starting an élite, it makes a lot of difference whether you are selecting from a very good level that has been attained and then are getting élite from that or whether your élite is made from very common, ordinary material.

The American Medical Association has contributed enormously to raising the level from which you are to make selection.

Now we will turn to the external form of the thing. Of course you have been broadcasted now so there are probably a lot of people in Brookline and other suburbs who have heard about your organization. It goes slowly. Of course you can try putting the initials on your cards, but I would go a little slowly on it because, you see, they might think you were a chiropractor. (Laughter) You can't be too cautious about these things. I remember very well a Methodist minister here in Boston, oh, a great many years ago, a young fellow. My father was a bishop, and I used to go around with him, and we visited some of these preachers. This preacher was very proud of his education. He was utterly without humor; he took himself very seriously, and he printed his degrees on his card—Rev. James B. Jackson, B.D.A.M. An old presiding elder came around. He was one of the old kind that hadn't been to college, but was a pretty hard-headed old boy with a real sense of humor. He looked at this card and said, "Jackson, you ought to get one of these colored colleges down South to give you the degree of Doctor of Divinity, then your card would read—"Rev. James B. Jackson, B.D.A.M. D.D." (Laughter)

You have to be very careful about degrees until the public has been educated.

The great difficulty about an élite is that it isn't an élite until a lot of people know that it is, because you see it exists really in the minds of other people. You may not know it, but if the public doesn't know it, what satisfaction can you get out of it? President Hadley said a thing years ago that has never been fully understood. He said, "You can never be sure that a law is really understood until the violation of it causes a man to be socially ostracized. When a man is put out of his club, then you will know that society is expressing a judgment." But you can refuse to answer questions.

Your cronies will go around and slap you on the back and say, "Go

ahead. The Senate be damned." That man doesn't care much what the great mass of the public think as long as his cronies stand around him and tell him to show disrespect for the elected representatives of the American people. It is what your cronies think and what the people whose opinion you care for means to you that after all counts, and so an élite that is going to be a real élite must be an élite than stands high in the opinion of the people that will be affected by the creation of the élite. That is going to take time. I hope the time will come when membership in your college will be a thing that people will know and understand. I know about it, and after you have gone a little while, when something happens to me next, I am going to ask my doctor why he doesn't belong to this society, because I am going to reach the point where I will refuse to have anybody look after me that doesn't belong to the society. (Applause) Isn't that the test? Isn't that what you are working for?

If I were taken down with what seemed like appendicitis in London, I would feel very much better if I were going to be operated upon by somebody who belonged to the Royal College of Surgeons, because I would know that he had been through one of the most rigid, absolutely impersonal and detached examinations as to his ability and that he had gotten through after this most careful scrutiny and therefore those letters after his name would mean so much to me that I would feel added satisfaction and confidence if I knew that he had been certified to in that way.

That is what we need in this country. Do you realize—of course you do, I needn't talk about it, but one of the great needs in America is an ability on the part of the public to discriminate in the choice of doctors and surgeons. That is the real test of intelligence, and little by little an organization like yours is going to help intelligent people to make selection.

You are not moved by any commercial ideas, you are not thinking at all of making yourselves more available and more desirable, your one aim has been and is to educate yourself and to raise yourself to higher levels to efficiency, and in due time a reasonably increasing intelligent public will realize you have achieved this and will feel more confidence in you.

In reality, what you are seeking in your organization is one of the most important and vital things for the American people. You are attempting to set ideals and standards. You are attempting to bring into comradeship —for after all that is what a college means; it means a group of colleagues with common aims and common purposes—a group of people who have had training, who are going on in self-education and in mutual education, who are growing day by day, who are attempting to keep pace with the rapid increase of knowledge and of skill which are made available for the public. You are trying laudably to create an élite, an élite based not upon tradition, an élite based not upon factitious or adventitious glory, but an élite based upon achievement, upon gradual, steady growth in knowledge and in power and in loyalty and in comradeship.

I offer you my heartiest congratulations. You have no illusions as to what you have set out to do. You do your work today and tomorrow and trust to others who come after you to take up the tradition and carry it on. I have little patience with a man who can't do anything until he sees the dawn of the millennium. My loyalty and admiration are for the men who do each day's work with a goal a little ahead, resolved to do as best they can, and to pass on an improved tradition to those who come after them.

May the College of American Physicians gain steadily, slowly but steadily, the position of a true élite in a democracy, an élite which claims prestige solely for honest achievement, for loyalty to science, for devotion to the welfare of the profession and to the service of the public. (Applause)

Serums and Vaccines in the Prevention and Treatment of Disease*†

By Benjamin White, Ph.D., *Boston*

THE present popularity of serums and vaccines rests upon the known efficacy of such time-proven products as smallpox vaccine and diphtheria antitoxin; partly upon the hope that some of the newer and less thoroughly tried products may ward off or modify a disease; or sometimes upon the very human wish that even if we are sceptical, we can at least be doing something for the patient.

As biologic therapy progresses it is fitting, and it may be useful, to make as careful and critical an appraisal as possible of the many serums and vaccines that are now offered to the medical profession. For such an appraisal we have several criteria upon which to base our judgment. There is first our knowledge of the chemical constitution and the physiological action of these agents and of the immunizing response they call forth when injected into the animal body, and then there is the clinical experience which has accumulated with their use. From the standpoint of theory we can predict with a considerable degree of accuracy the general effects which may follow the injection into the body of foreign proteins such as those in bacterial vaccines and in horse or other animal serum products, although we may not have a complete explanation of their actual mode of action. Furthermore, we have acquired a great deal of reliable information about the nature and extent of the protective or immune mechanism that functions as a result of the parenteral introduction of viruses or inanimate protein matter. To be sure, there remains much unexplained detail in these immunological processes and many phenomena which have not yielded to our present methods of study, yet we possess sufficient sound knowledge to say what one might or might not expect from the immunizing action of this or that serum or vaccine. When we draw upon clinical experience for our estimates, however, we must limit ourselves to mass or prolonged experiences or to carefully studied parallel series of cases treated with serum or vaccine and similar cases in which there was no such treatment.

Speaking in a general way we may safely say that one might expect vaccines or similar antigens to produce more or less active immunity and, therefore, some specific resistance

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†From the Antitoxin and Vaccine Laboratory of the Massachusetts Department of Public Health.

against the particular disease represented by the vaccine or antigen; and that in acute disease they would have little curative effect beyond whatever possible beneficial physiological action may come from their alien protein nature. With serums one could reasonably say that a potent serum would protect against related infection from a recent exposure or, for a short while, from imminent exposure, or would confer upon the recipient temporary specific resistance against an already existing infection. The possible action of serums and vaccines in diseases due to causes other than infective agents is still on such a speculative basis that any consideration of this kind of therapy may be omitted here.

With these general principles in mind, the various vaccines and serums usually employed in the prevention and treatment of infectious diseases may be discussed as follows:

A preliminary definition of terms may serve to excuse certain seeming inconsistencies. Under "vaccines" are included preparations containing viruses, either living, attenuated or dead, the products of bacterial metabolism such as toxins and so forth, and proteins of non-microbic origin, as those from pollens and food-stuffs. For the present purposes this term applies to these agents whether they be used to determine susceptibility or resistance to infection (Schick toxin, Dick toxin, and some tuberculins); to produce active immunity to anticipated infection (vaccine virus, typhoid vaccine, Dick toxin and diphtheria toxin-antitoxin mixtures); or to exert a curative action where infection has already taken place or infectious disease exists (rabies vaccine and some bacterial vaccines). "Serums" might embrace the blood serum of normal animals; the serum or refined serum globulins of animals immunized against toxins (antitoxic serums, such as diphtheria or tetanus antitoxins), or of animals immunized by the injection of bacteria or their products other than toxins (antibacterial serums, as antimeningococcic serum and pneumococcus antibody solutions amongst others). Such use of these two names, loose as it is, can be said to be far more accurate than their usual employment.

I. VACCINES

The efficacy of a given bacterial vaccine for prophylaxis may be forecasted with some assurance. If the organism used belongs to a homogeneous group, such as Type I pneumococcus or typhoid bacilli; if it is capable of producing readily a definite stimulation of antibodies; if the titre of antibodies so produced is maintained at a reasonably high level over a worth-while period; if the disease is a manifestation of bacterial invasion as distinguished from toxemia; and if the vaccine is not of itself so toxic as to preclude its use; then we may expect that a suitably prepared vaccine of this organism will be of value. A low rating in any one of these particulars, on the other hand, may be sufficient to render the vaccine useless as a prophylactic. When these vaccines are used for their specific or non-specific therapeutic effect, considerations similar to those just mentioned apply to such use.

1. *Acne.* The acne bacillus has been shown by experiment to have a low antigenic coefficient, and one

therefore would not count on it in vaccine form to produce marked effect upon any infectious process caused by it. Vaccines made of suspensions of this bacillus, either alone or combined with the usual skin cocci, have been employed in the treatment of this obstinate condition. It has been recommended that they be used in fairly large doses in conjunction with appropriate treatment of the skin and with general hygienic and dietetic measures. Even then their curative effect is not particularly notable. Persistent vaccine treatment, however, may benefit cases that have not yielded to other treatment, and in those patients where no improvement follows it is possible that there may be biologic differences between the strain or strains injected and those infecting.

2. *Allergy to Food and Pollen Proteins.* Hypersensitiveness to foods, plants, dust, dander and a host of varied substances presents a wide field for exploration. Already we have a bewildering list of preparations—the so-called "allergins"—for diagnosing and treating these various states of hypersensitiveness. Their number, and the complexity of the problem may excuse the omission of their discussion at this time.

3. *Antivirus (Besredka).* Besredka has proposed the use of sterile filtrates of broth cultures of staphylococci, streptococci, colon bacilli, gonococci and other organisms for local application or irrigation in infections due to these various bacteria. His theory is that the growth of such microorganisms produces in the broth substances specifically antagonistic to the species; and that these substances when applied to the infected tissue inhibit the growth of the causative organism. These products are manufactured by many of the European laboratories, but both laboratory experiment and clinical trials by competent observers in this country have, in the main, given disappointing results.

4. *Catarrh, Common Colds and Influenza.* For both acute and chronic infections of the upper respiratory tract a number of vaccines are offered, containing a few or many of the following bacterial species; influenza bacilli, streptococci—both hemolyticus and viridans—, the three types of pneumococci, Friedländer bacilli, Micrococcus catarrhalis and staphylococci (aureus and albus). There is little scientific basis for using such polygenic mixtures to prevent infections of such uncertain etiology. Their use, of course, is directed against secondary invaders, but even then we should expect that the Pfeiffer or influenza bacillus, Micrococcus catarrhalis and the streptococci would produce little or no immunizing effect, although pneumococci might establish a slight, transient immunity. These vaccines are widely used, and many clinicians claim that where no anatomical abnormality or pathologic lesions are present their vaccinated patients usually escape the common respiratory infections. During the 1918-1919 pandemic of influenza and subsequently, studies have been made on several large groups to determine the immunizing value of influenza and allied vaccines. In these groups, approximately one-half of the number of subjects were vaccinated and the other half not vaccinated. McCoy, after analyzing the incidence of

acute respiratory disease in some of these groups failed to find any evidence that the vaccinated persons fared any better than the unvaccinated.

5. *Asiatic Cholera.* Bacterial vaccines made from the cholera vibrio are antigenically potent in producing a fairly high degree of resistance to this disease. This immunity is neither absolute nor enduring, yet when kept at a proper level by semi-yearly or yearly vaccination it suffices to give excellent protection to troops and travellers, to physicians and nurses, and to members of communities where the disease is endemic. Some of our commercial laboratories offer this product with conservative claims in regard to the duration of the immunity produced.

A novel and apparently reliable means for preventing Asiatic cholera is the use of the bacteriophage as proposed by d'Herelle. This agent obtained from sewage or from cultures of cholera vibrios and other organisms has the ability to dissolve these vibrios both within and outside the body. When the proper "phage" is added to polluted water supplies it reduces the number of virulent cholera organisms to such a low point that the water is practically incapable of causing infection and, when given to man by mouth, this same phage will dissolve many of the vibrios ingested and prevent their multiplication in the intestine. The results of d'Herelle's work in India will be watched with the greatest interest, because if successful his method provides a simple and cheap way of rendering polluted water safe and also of protecting the individual.

6. *Colon Bacillus Infections.* Because Bacillus coli and other bacilli of the Paracolon group are found in many infections in or about the gastro-intestinal and urogenital tracts, vaccines made from these organisms are used in their treatment, and sometimes before surgical operations to prevent infection. Bacilli of this type have the peculiarity of inducing an immunity specific for the one strain injected and it seems unlikely that whatever immunity might follow the injection of a stock vaccine would cover the many strains encountered in these varied conditions. One's chances of success, therefore, would appear greater with the use of autogenous vaccines, but even here it may be questionable if any improvement in the patient's condition may not be due to some accompanying form of treatment.

7. *Combined Vaccines.* Any vaccine composed of B. coli, Pneumococcus I, II and III, Streptococcus (hemolyticus and viridans), Staphylococcus albus, Staphylococcus aureus, Staphylococcus citreus, recommended in cellulitis, phlegmon, septicemia, puerperal sepsis, abscesses and other septic conditions would seem to be a decidedly hit or miss form of treatment. Now that competent bacteriologic service can be so easily obtained, there seems no need for neglecting the diagnosis or for injecting such a bacterial mixture in the hope that it might fit the case.

8. *Diphtheria Toxin for the Schick Test.* The skin reaction, or absence of it, to the intradermal injection of diphtheria toxin is an accurate index of susceptibility or resistance to diphtheria. If the results are to be reliable, however, only fresh Schick outfits, kept continuously cold should be used.

and the exact amount of diluted toxin specified in the directions accompanying each outfit should be carefully injected superficially into the skin. With close attention to these details the technical error should be two per cent or less. This test should *always* be made on persons receiving toxin-antitoxin injections six months after the last injection of this mixture. Other methods recommended for the routine determination of immunity to diphtheria in human beings possess no advantages over properly done Schick tests.

9. *Diphtheria Toxin - Antitoxin Mixture, Toxoid, Anatoxine.* With such efficient means for producing active immunity to diphtheria it seems inexcusable to permit children to pass from infancy without this protection. The one-tenth L plus toxin-antitoxin mixture given subcutaneously in three doses one or more weeks apart will immunize the great majority of those so treated. The dose should be exactly that given in the directions. The ensuing immunity should always be checked by a Schick test performed six months after the last injection and should the test be positive a further course of toxin-antitoxin should be given and the person again retested.

There has been much discussion about the action of toxin-antitoxin mixtures in sensitizing to horse serum proteins. They undoubtedly do render some of the recipients allergic, but it is doubtful if the degree of hypersensitiveness so produced leads to harmful results when such a sensitive person has later to be given any other product of horse serum. An accelerated or aggravated attack of serum sickness may occur in such an instance, but it hardly seems advisable to replace horse antitoxin in the toxin-antitoxin mixture with antitoxin made from the goat or sheep. As a matter of fact, toxin-goat-antitoxin mixtures have been found in some cases to cause more severe local reactions than does the usual product.

The ideal immunizing agent would be one containing diphtheria toxin robbed of its toxic but retaining its antigenic properties, and one giving few, slight or no reactions. This ideal is being approached with the development of the so-called "Toxoid" or "Anatoxine." These preparations in which the toxin is detoxified with formalin are harmless, have high immunizing value and give rise to no reactions in younger children. They do, however, cause local or general reactions in persons sensitive to diphtheria bacillus protein, and therefore, should not be administered to persons over five years of age unless the individual shows no pseudo element in the Schick test or a negative reaction to an intradermal injection of the toxoid or anatoxine. Persons reacting positively to either of these tests may be given either toxin-antitoxin mixture or toxoid in a longer series of divided doses.

10. *Gonococcus Vaccine.* Such vaccines have been widely used in both acute and chronic gonorrhoea and its complications, but usually with disappointing results. Like other Gram-negative cocci, the gonococcus is capable of stimulating only a low grade immunity, and it is not to be expected that in a vaccine it would arrest the acute process or influence deep-seated

lesions. In Europe, this vaccine is administered in the early stages with the belief that subsequent localization of the gonococcus will be prevented.

11. *Pertussis.* There is much debate about the value of vaccines made from the Bordet-Gengou bacillus, alone or mixed with various bacteria common to the upper respiratory tract, in the prevention of whooping cough. Laboratory experiment has shown that B. pertussis is a feeble immunizing agent, and, therefore, one would anticipate that its injection would, at best, give only a slight immunity, so slight, that infection would rarely be prevented, but perhaps sufficient to strengthen somewhat the body's natural resistance to the effects of the disease. This anticipation is fulfilled in practice. The value of the secondary organisms in the mixed vaccines is subject to the criticisms made under catarrhal vaccines. Many physicians still hopefully administer this vaccine routinely to all children exposed to whooping cough, but the results, so far as protection goes, are not impressive. Quoting from a previous article by the author, "Clinical reports as to the ability of vaccine treatment to prevent or mitigate an attack of this disease are not in agreement. The majority of these reports are uncontrolled and, therefore, the worth of their evidence should be discounted. The Danish reports are favorable as is also the report of the Harvard Whooping Cough Commission. A critical analysis of the latter report, however, shows an absence of proper controls and that the results obtained with the vaccine were not clear cut or convincing. In other series of observations extending over a period of several years where children were vaccinated with small and large doses of fresh and old vaccine and where alternate unvaccinated children were used as controls there was no appreciable difference in the whooping cough experience between the vaccinated and unvaccinated children.

"While there are many enthusiastic users of pertussis vaccines, the whole evidence would seem to indicate that such vaccines, whether simple or combined, are of doubtful value, and rank low in the list of biologic agents."

12. *Plague.* Although one attack of plague usually confers a life-long protection upon the survivor, vaccines made from Bacillus pestis confer only an incomplete and transient immunity. McCoy and Chapin state that there is no evidence that such vaccination has ever controlled an epidemic. However, because of the deadly nature of this disease the individual who may be exposed to it might seek such protection as these vaccines afford. The best known of them is the Haffkine, although those prepared by other methods are probably equally as good. It should be remembered that the plague bacillus is toxic for human beings and accordingly one may look forward to systemic reactions of some severity following the injection of this vaccine.

13. *Pneumococcus Vaccines.* Experiences with pneumococcus vaccines for the prevention of lobar pneumonia both in private and military practice have not been encouraging. On the other hand, the work of Goodner and that of Barach, indicate that the injection of heat-killed pneumococci into the body sets up a definite immunity to the type of pneumococcus injected.

This immunity lasts for only a short time (probably less than two months) but where the disease is uncommonly prevalent, or for persons particularly susceptible to it, the frequent injection of a vaccine containing the three main types may serve to avert an attack.

14. *Rabies Vaccines.*

a) *Human.* The increase of this disease in this country brings more and more inquiries as to the best vaccine to use and the preferred manner of administration. Rabies vaccine, whether it be the attenuated living virus made by the classic method of Pasteur, the diluted living virus of Högyes, the dialyzed preparation of Cumming, the dried virus of Harris or the phenolized virus of Semple, when used soon after the patient is bitten may be counted on to prevent the disease in nearly every case. When the wound is severe, when the bites are multiple or when they occur about the head and face, treatment should be begun at the earliest possible moment and the full course of twenty-one injections should always be given. In some of the European countries vaccinal treatment is given only at designated institutes where the patient is hospitalized and guarded against physical or emotional stress for the purpose of reducing the possibility of post-vaccinal myelitis or paralysis. Happily such sequelae are rare, but they do sometimes occur and precautions should be taken to guard against them. One of the conclusions reached at the last International Rabies Conference (1927) was that, "Such paralytic accidents are less frequent if glycerinated or carbolised vaccine be employed."

b) *Canine.* Inasmuch as human rabies in this country usually comes from the bite of a rabid dog, quite as important as treating a human case is the prevention, if possible, of rabies in dogs. Special vaccines, made by the Semple method, are being strongly advocated for the routine immunization of dogs, and some health officials would make their use compulsory by law. Unfortunately these vaccines frequently fail of their purpose, because dogs given one, two and three injections of the carbolized vaccine have later developed rabies, and, sometimes because of their owners' feeling that the vaccine treatment had made rabies an impossibility, diagnosis has been delayed and the animal has been allowed to be a menace until the symptoms became unmistakable. Reference to Semple's original article should convince one that a single injection, or even two or three injections of such a vaccine can hardly be counted on to make dogs invulnerable to the disease.

15. *Rocky Mountain Spotted Fever.* The Federal Public Health Service has announced that a vaccine against this disease may be obtained free of charge by application to the United States Public Health Service Laboratory at Hamilton, Montana. Ranchmen, prospectors, and students investigating this disease can now protect themselves against this infection.

16. *Scarlet Fever Streptococcus Toxin:*

a) *For the Dick Test.* Recent improvements in the preparation of this product in broadening its polyvalency by including the toxins of more strains of scarlatinal streptococci, by increasing the amount of toxin for the skin test dose and by

buffering the toxin dilution, thus making it more stable, have all operated to increase the reliability of the Dick test. This toxin can, therefore, be used with greater assurance than heretofore that a positive reaction to the test indicates susceptibility to the disease—a negative reaction, insusceptibility.

b) *For Active Immunization.* These improvements in the preparation of the toxin, and modifications in the manner of its administration enhance the value of this product for prophylactic purposes. The Dicks now recommend a graduated series of five injections of 500, 2,000, 8,000, 25,000 and 80,000 skin test doses of toxin at weekly intervals. Such a course is claimed to produce an immunity to scarlet fever in over 95 per cent. of those so treated and one which persists for at least three years. The schedule of Young, consisting of bi-weekly injections of 500, then 3,500 and finally 25,000 to 30,000 skin test doses reduces the number of injections by two and appears to be equally efficacious. This toxin may sometimes give rise to a constitutional reaction, simulating the early symptoms of scarlet fever. To avoid such occurrences it is advised that castor oil be given before the injections which, furthermore, should be made when the stomach is empty. A second Dick test to determine the development of immunity should follow sometime after the last injection of toxin.

The application of the Dick test and active immunization to nurses and those likely to be exposed to scarlet fever has proven a successful way of protecting them. On account of the present mildness of the disease and the long series of test and immunizing injections, it is questionable if it is profitable to extend this method to larger groups such as institutional or school children.

17. *Smallpox Vaccine Virus.* The first vaccine to be discovered, and the one longest and most extensively used, vaccine virus stands as one of the most valuable immunizing agents man has yet devised. Immunologically considered it should be an efficient prophylactic. Being the living virus of vaccinia or cowpox it is closely related to the virus of variola, and it creates much the same train of physiological processes that operate in a mild case of smallpox, resulting in a prompt and more or less lasting protection against that disease. Being a living virus it should be given all the care in preservation and handling that its manufacturers bespeak for it: Fresh lots only should be used and they should be kept continuously at a temperature below 5° C. Again quoting from a previous paper by the author, "In order to obtain the best results, strict attention should be paid to the method of vaccination which is described in the leafllet accompanying each package of the vaccine distributed by the Massachusetts Department of Public Health, and which has also been published by Leake and by White.

"The older methods of cross hatching, incision and linear scarification should be abandoned, and the simple, painless and wholly satisfactory technic of multiple pressure be used instead. The method of single or multiple puncture is not to be recommended because recent reports show that undesirable results may follow. Vaccina-

tion by intradermic injections, as lately advised by Toomey and Hauver, holds dangerous possibilities and should not be used.

"When vaccinations are performed by the multiple pressure (Kinyoun) method, no dressings should be applied to the vaccinated site and under no circumstances should shields or tight bandages be applied. Shields are an abomination and their manufacture should cease. Vaccination should always be performed on the arm and never on the leg. If any untoward reaction occurs, if the vesicle or pustule is injured or broken, or if the scab comes off prematurely, the vaccination wound may be painted with tincture of iodine or a 4 per cent alcoholic solution of picric acid, which if applied more than 48 hours after vaccination will not interfere with the development of immunity. Then such care as is indicated should be promptly given.

"Too great stress cannot be given to the importance of vaccination technic. Fresh virus, applied by the multiple pressure method will give a maximum of "takes" in first vaccinations, a maximum of accelerated "takes" or immune reactions in revaccinations, with a minimum of discomfort and undesired results.

"Careful attention, especially in revaccinations, should be given to the appearance of vaccinoid or accelerated "takes," and of immune reactions. The vaccination site should, therefore, be observed on the third day and twice later, usually four and eight days after vaccination. The various reactions following vaccination have been excellently described by Hooker and also by Leake.

"The ideal plan for vaccination is to vaccinate babies during their first year of life and again before entering school. During epidemics and where definite exposure is known to have taken place revaccinations should be performed.

"Smallpox vaccines, other than the present dermo-vaccine obtained from calves have been put forward with claims of superiority. The testicular vaccine of Noguchi, the neuro-vaccine of Levaditi and various vaccines treated with a variety of chemical agents have been tried and some of them are in use in different parts of the world. They appear to possess no distinct advantages over the calf vaccine and at present are not to be recommended."

18. *Staphylococci.* Ever since Wright's first treatises on bacterial vaccines, those made from staphylococci, particularly the albus and aureus, have been considered as having definite therapeutic worth for treating and preventing the recurrence of local infections due to these organisms. In the case of furuncles, carbuncles or other abscesses, vaccine treatment seems to hasten maturation and healing. In the indurated or burrowing infections so typical of S. aureus, persistent treatment preferably with an autogenous vaccine often checks the progress of the disease and prevents relapse. In septicemia due to these cocci it is difficult to see why the introduction into the already infected body of additional cocci, even though killed, should benefit the condition. It has been claimed that in such cases the

septicemia has been aborted or that sterilization of the blood stream with localization of the infection has taken place. But such sometimes is the course of general sepsis under merely supportive treatment.

19. *Streptococci.* The immunologist looks for a definite but not marked immunologic response on the part of a body injected with killed streptococci, a response specific for the biologic groups administered and sometimes specific only for single strains. Streptococcal infections of the sinuses, the middle ear, mastoid process and endocardium have generally been found to resist vaccine treatment, and what has just been said about staphylococcus septicemia applies equally well to sepsis with streptococcus. Where it is desired to prevent secondary infection from these cocci the use of a vaccine of wide polyvalency might result in some basic immunity. However, in using such a vaccine one should bear in mind these limitations.

20. *Tuberculins and "B C G."* For revealing the existence of tuberculous infection the intradermal injection of Old Tuberculin ("O. T.") by the method of Mantoux is our most discriminating test, although as in other tuberculin tests, a positive reaction may mean either healed infection or active disease. As the incidence of tuberculosis continues to decline, and as opportunity for infection decreases, this test will acquire greater and greater clinical significance. For the treatment of tuberculous disease Old Tuberculin, Bouillon Filtrate ("B.F.") and the Bacillus Emulsion ("B.E."), used singly or in combination should suffice so far as antigenic spread is concerned. Ophthalmologists, almost universally, prefer the Tuberculin Residue ("T.R."), which has much of the antigenic value of "B.E." without some of its disadvantages.

The medical world is now engaged in discussing Calmette's "B C G" as an immunizing agent against tuberculous infection. This preparation is made from a living culture of a strain of bovine tubercle bacillus degraded in virulence by long, successive cultivations in a bile-containing medium. Calmette claims that, being robbed of its virulence and invasiveness, it produces a benign local lesion which stimulates anti-tuberculosis immunity. It is given to infants by mouth in the first days of life, or it may be given subcutaneously. Extensive clinical studies have been under way in Europe for some years and if the statistical data could be taken at their face value, it would appear that children and also young cattle treated with "B C G" have escaped tuberculous disease in far greater proportion than their unvaccinated neighbors of corresponding ages. Petroff, however, has challenged the harmlessness of this vaccine and reports that he has dissociated this culture into both virulent and non-virulent strains. This possibility has been denied by French workers but until this very important question is decided, it would seem wise to be cautious. From what we already know of immunity in tuberculosis, such a vaccine, even if it is innocuous, and even if it should be absorbed from the intestinal tract and find lodgement in a lymph node setting up a localized tubercle, would at most bring about only a low grade immunity to infection

by the tubercle bacillus. Such a scant, acquired resistance may augment the body's natural defenses sufficiently to retard extension of the infective processes, but until more convincing evidence appears and until the children already vaccinated reach the age of greatest vulnerability to tuberculous disease, any dogmatic opinion may wisely be withheld.

21. *Typhoid and Paratyphoid Bacilli.* Among the first bacterial vaccines to be devised, vaccines made from the typhoid bacillus and lately from this bacillus combined with Salmonella paratyphi (B. paratyphosus A) and S. schottmülleri (B. paratyphosus B) have more than justified their early promise. Absolute immunity to typhoid and paratyphoid infection does not result from the usual course of three injections, nor does this immunity persist for any great length of time, yet one series of three injections usually protects against any but a massive infection, and this protection can be continued by yearly injections where the typhoid hazard is great, or by bi- or tri-yearly injections where the chance of exposure is no greater than that confronting those who care for the sick. By injecting in divided doses at weekly intervals until a full two and one-half cubic centimeters are given, both local and constitutional reactions in adults may be avoided. Besredka advocates the administration of such vaccines by mouth, not only for the purpose of avoiding reactions, but more especially for the theoretical purpose of applying the immunizing antigen directly to the tissue liable to infection. This idea may appear fantastic or not according to one's viewpoint. Recent experimental studies show that specific agglutinins, precipitins and complement-fixing antibodies appear in the blood of persons to whom the triple typhoid-paratyphoid vaccines have been administered orally, arguing therefore for the creation of an active specific immunity. Those so-called "Entero-vaccines" are offered by many of the European laboratories, but in this country we have been content to wait until further favorable information is forthcoming.

22. *Other Vaccines.* The above list, while incomplete, includes the preparations that are most commonly used. Manufacturing laboratories in various countries supply vaccines or similar products for the prevention and treatment of asthma, erysipelas, ozena, pyorrhoea, rheumatism, rhinoscleroma and other conditions, infectious and otherwise. Since to these products it is not possible to apply our present standards of appraisal, they may be left out of consideration.

Summary

If we disregard those vaccines which fail to reach our standard of evaluation based either on scientific measure or on the result of reliable and controlled clinical experience, the list dwindles. There is left, however, an array of products of incalculable worth for the prevention of infectious disease. It would seem from the answers to Hektoen's questionnaire that physicians out of their personal experience, are practicing a somewhat similar process of elimination. With the passing of fads, by the application of strict criteria, and after the further accumulation of clinical results, some

of the preparations now on the market will fall into disuse, with a gain to the patient in accuracy of diagnosis and soundness of treatment.

II. Serums

In appraising serums on the basis adopted in discussing vaccines we can prophesy what their general physiological action will be and, with far greater conciseness than is possible in the case of vaccines, just what immunologic effect to anticipate. Knowing that serums may contain approximately from six to eleven per cent of proteins (globulins and albumin) and that concentrated serums may contain from ten to nineteen per cent of globulins, and knowing the allergic status of the recipient we can usually foretell the constitutional response to their injection and avoid many of the disturbing reactions that follow their administration to serum-hypersensitive persons. There still remains the little-understood realm of the non-specific stimuli of which serum proteins are capable. In the case of immune serums, close acquaintance with what we may call the philosophy of the disease coupled with familiarity with the immunologic nature and antibody content of the antitoxic or antibacterial serum will indicate beforehand the possible value of the treatment in any given case. Such knowledge teaches us the limitations as well as the applications of this class of biologic products. Stated in general terms, a potent serum corresponding immunologically to the infection to be treated, given in sufficient dosage early in the disease should, if no serious complicating factors exist, be of the greatest aid in bringing about recovery. The value of the serum will decrease as the dose is diminished from the proper level or as the disease progresses. It should be borne in mind that the injection of foreign protein, especially in the amounts represented by the average serum dose, alters the individual's physiological response to subsequent injections of a similar protein. For this reason the free use of antitoxic or other serums, unless the condition strongly warrants their administration, should be deprecated. It should be further remembered that the passive immunity conferred by heterologous immune serums is of short duration, lasting only some two weeks or more and that the period of protection is even shorter in the case of patients who at some previous time have received injections of horse or other foreign serum products. So, too, will the time of appearance and the level and persistence of the immunity depend upon the route of administration. For a further understanding of the curative value of this class of products it may be mentioned that with most antitoxins, laboratory tests give an accurate estimate of their actual immunizing value, but with antibacterial serums the parallelism is by no means so close. This is because of the difficulty of reproducing in suitable experimental animals such infectious diseases of man as pneumonia or meningitis, although such toxemias as diphtheria and tetanus may be approximated closely enough in guinea pigs and other common laboratory animals.

1. *Antianthrax Serum.* When the anthrax lesion is in the skin and underlying tissues the prompt and intelligent use of surgery is often sufficient.

When such an infection has progressed, or when it exists in the lung or alimentary tract the use of anti-anthrax serum will reduce the chances of a fatal outcome. Fortunately, such a serum is now available and should be used according to directions in all infections due to the anthrax bacillus.

2. *Anterior Poliomyelitis.* The rationale for the use of convalescent serum in this disease appears to be sound. Recovery from an attack brings a life-long immunity; the serum from a recovered patient neutralizes infectious brain and cord in vitro; and it protects monkeys against what would otherwise be a fatal dose of such virus. Now that some monkeys, especially *Macacus rhesus,* can be infected with poliomyelitis virus by injecting them with the brain or cord from a human case, the way has been opened for testing human convalescent or other serum for protective action. Both Flexner and Aycock with this method have shown that the blood serum of many adults contains substances antagonistic to the virus, while the serum of persons convalescent from poliomyelitis has such an appreciable protective action that one would expect such a potent serum given early and in sufficiently large doses would stay the course of the disease. While the results following treatment of sporadic cases can be considered as being no more than suggestive, Aycock's analysis of the results of the Massachusetts cases treated in 1927 and 1928 gives us the first statistical evidence of the benefits of this form of treatment. When the serum was given in the first stages of the disease before serious cellular impairment had taken place recoveries and freedom from crippling sequelae were far more frequent than was the case of patients who received no serum. From the very nature of this disease with the damage to the cells of the brain and cord, one would expect that this serum would be of value only in preventing further development of the infectious process and would have little or no curative action in remedying any cellular impairment already present. Early diagnosis and prompt treatment, therefore, are essential if any measure of success is to be expected. For the preparation of this serum, the blood should be drawn if possible from a person convalescent from poliomyelitis, the serum separated, clarified and tested for potency and for sterility, and then injected into the patient both intraspinally and intravenously. Aycock advises that about 15 to 20 cubic centimeters of the serum be administered by the spinal route and twice the amount into a vein.

Serums produced by the artificial, active immunization of horses with streptococci have been tried and claims made of therapeutic efficacy, yet when tested for virucidal action they have been found lacking in protective power.

3. *Antidysentery Serum.* Polyvalent serums made by actively immunizing horses with the Flexner, Shiga and other strains of the dysentery bacillus are useful in the treatment of bacillary dysentery only, and their value varies in inverse ratio to the length of time that has elapsed since the onset of the attack.

4. *Anti-gas-gangrene Serum.* Because the bacteria causing this type of

infection, such as Clostridium welchii, Cl. oedematiens, Cl. oedematis-maligni and others, produce their characteristic effects through the toxins they elaborate, the treatment of these conditions with a serum containing specific antitoxins is logical. Such antitoxic serums are obtainable from a few of the manufacturing laboratories, and along with appropriate surgical measures are indicated in treatment.

5. *Antigonococcic Serum.* Inasmuch as gonococcus apparently produces no soluble toxin, the most that could be hoped for in our present state of knowledge, would be the production of a serum containing antibacterial substances for this organism. While serums are available that contain specific agglutinins, complement-fixing and other antibodies, their immunologic reactions in vitro are not of a high order, and their therapeutic action is uncertain.

6. *Antimeasles Serum.* Many and varied have been the bacteria that have been described as being intimately associated with measles if not the cause of it. Attention now, however, is almost entirely directed to the green diplococci first described by Tunnicliff, and the more or less similar streptococcus of Ferry and Fisher. These cocci have been found in the blood and throats of patients in the early stages of the disease. So far as can be discovered from the literature the critical test for etiological relationship by producing the disease in a susceptible person by inoculation with a pure culture has not been tried. Under suitable cultural conditions these cocci have yielded a toxin which is said to have the same relation to measles immunity as does diphtheria toxin in the Schick test or scarlet fever streptococcus toxin in the Dick test. This extracellular toxin is neutralized by the serum of measles convalescents.

These facts warrant the attempt to prepare an artificial immune serum as well as support the use of convalescent serum for prophylaxis. Tunnicliff has, indeed, succeeded in immunizing goats to the toxin of her diplococcus, as proved by careful laboratory experiment, and, in the hands of Hoyne, Gasul and Halpern this immune goat serum has been found to prevent or modify measles in susceptible persons exposed to the disease. A similar serum has been obtained from the horse by Tunnicliff and White, which in vitro compares favorably in its immunological behavior with immune goat or convalescent serum. Further clinical trial is necessary before passing judgment on these new products. While there is ground for hope that such serums may protect temporarily against infection or mitigate the disease when given in the prodromal period, there is no indication that they would be of any avail in treatment.

Degkwitz believes that measles is caused by a filterable virus, often associated with a green-producing coccus. He claims to have cultivated this virus and with it has produced an immune serum from the sheep. This serum has been put to clinical trial, but the reports are contradictory.

"Convalescent serum, however, (to quote once more from a previous discussion) may be accepted as a valuable agent in preventing measles, or better for modifying an attack so that the patient while being spared any harmful

effects of the disease is permitted to develop an active and presumably lasting immunity.

"There are difficulties in obtaining an adequate supply of this convalescent serum, but the difficulties are not insuperable unless large numbers of exposed persons are to be treated. The blood should be taken only from individuals who are definitely known to have had measles and then as *soon after convalescence* as possible. Should such a source of supply be lacking the blood of persons with a history of previous measles may be used. The usual strict precautions to be observed in the case of all human serums, such as the donor's freedom from communicable disease, and the sterility of the serum, should be observed.

"Richardson and Jordan advise a dose of from 6 to 10 cubic centimeters, given intramuscularly. When injected within the first four or five days after exposure (counting two days additional from the date of the appearance of measles in the person to whom the contacts were exposed) the disease is usually prevented. When given later this dose generally prevents a severe attack but may allow a mild form of the disease to develop, which establishes a lasting active immunity. The dosage cannot be accurately determined because serums vary in their protective power. The age and size of the person receiving the serum also influence the amount to be injected. In general, it may be said, that at the present time convalescent serum is a valuable agent for protecting young and susceptible children against a malady, which without the serum may cause harmful and sometimes fatal results."

7. *Antimeningococcic Serum.* A former discussion of this serum by the author may be repeated here. "In epidemic cerebro-spinal or meningococcus meningitis the use of antimeningococcic serum has brought about a marked reduction in fatality and in the physical damage that follows such infections. Its administration is indicated in every case of meningitis due to meningococcus and may be given to advantage in many cases before a definite bacteriologic diagnosis has been established. All such serum produced in laboratories under the supervision of the United States Hygienic Laboratory is polyvalent, and contains antibodies for strains of the various agglutination and tropin groups. It should always be administered subdurally and at the earliest possible moment. When injected into the spinal canal the dose should be slightly smaller in amount than the spinal fluid withdrawn, and it should be injected slowly and under gravity pressure—not by syringe.

"The serum may also be injected into the ventricles, but this route is not commonly chosen except in severe or obstinate cases. Its injection into the *cisterna magna* is comparatively free from danger and is recommended by Ayer and others, particularly in child patients. The intravenous injection of the serum, advocated by Herrick and others, may be of benefit but theoretically at least, only in early stages of the disease. Directions for continued serum treatment can be found in text books and in circulars accompanying the product.

"The practitioner should bear in mind that from year to year or where the infection is brought from other

countries, the strain or strains of meningococcus causing the infection may be of a type not covered by the usual serums. In every case of meningococcus meningitis, wherever possible, the organism present in the spinal fluid should be isolated and carried under cultivation. Then, should the patient fail to respond satisfactorily to treatment with the particular preparation used, it may be possible by simple agglutination tests to select another lot or make of serum which will have a higher antibody content for the strain involved. The serum treatment of meningococcus meningitis should, therefore, always be accompanied by careful bacteriologic and serologic control."

8. *Antiplague Serum.* The plague bacillus is notable for the highly poisonous nature of its protoplasm and for the severe toxic effects that accompany the disease in man. In preparing a therapeutic serum, therefore, the plan of immunizing horses is to develop both antitoxin and antiendotoxin. The method of Yersin is the one employed in making this product. Rosenau says of the Yersin serum, "At most this antitoxic serum is weak; it has feeble and transient protective properties, and doubtful curative power. Very large quantities must be administered in the disease to obtain any effect at all."

9. *Antipneumococcic Serum.* Long-continued laboratory study has proved that the introduction of dead pneumococci (of Types I and II, at least) into the animal body leads to an active immunity as shown both by resistance to subsequent infection and by the presence of agglutinins, protective and other antibodies in the serum of such an animal. With due allowance for its limitations it can be said that antipneumococcic serum, Type I, prepared according to the original or modified method of Cole, administered in full doses within the first three days of the attack frequently checks the disease and reduces its fatality. Antipneumococcic serums for Type II, III and IV infections has been found to be clinically valueless, a fact which squares with laboratory experience. By improving the methods for horse immunization and by separating out and concentrating the protective substances, preferably by the method of Felton or that of Banzhaf, we now have "Pneumococcus Antibody Solution," which in the hands of Cecil, Park, Bullowa, and Lord, among others, has shown definite curative action in cases of Type I lobar pneumonia and a somewhat less but still favorable effect in Type II infections. In pneumonias due to pneumococci of Types III and IV, this antibody solution has been of very doubtful benefit. The lessening of the number and severity of attacks of serum sickness is one of the gains accruing from the concentration process. This remedy is still on trial but is now procurable in the market.

10. *Antirheumatic Fever Serum.* Experiences of the past year have brought nothing to modify the author's earlier opinion, "Although some late publications, notably those of Small and of Birkhaug, give the idea that the riddle of rheumatic fever is solved, the solution is neither so simple or sure. Here it is claimed that a particular coccus is the cause of the disease and its train of distressing and

obstinate symptoms. A toxin is said to have been produced which, used in intradermic tests, denotes susceptibility or immunity to the disease, but the evidence is neither clear nor convincing. Here, too, an immune serum has been obtained about which widely diverging reports are heard. It is by no means certain that "Streptococcus cardioarthritidis" is the cause of rheumatic fever, and we must await the results of further investigation before passing judgment on the biologic agents now available."

11. *Antistaphylococcus Serum.* Although Parker and others have demonstrated toxin production by staphylococci, the serums at hand are essentially antibacterial in nature. One would expect no more of them in the way of curative action than from antigonococcic serum.

12. *Antistreptococcic Serum.* Postponing for the moment any discussion of the streptococcal antitoxins, antibacterial serums specific for streptococci may be considered. These are made for treatment of infections due to Streptococcus hemolyticus and also S. viridans. From our knowledge of antistreptococcal immunity in general we would rate these serums low in immunizing value. The occasional favorable reports from their users encourage their continued manufacture.

13. *Antivenins.* Antiserums specific for venoms of the American rattlesnake, copperhead and water mocassin are now manufactured in the United States. Laboratory trials show that such serums not only neutralize these venoms in the test tube but protect animals injected with killing amounts of venom. When injected into human beings bitten by any one of these three poisonous snakes, if given soon after the bite is received, they prevent or modify the toxic symptoms. The shorter this period the more useful is the antivenin. In other lands various institutes and manufacturing laboratories prepare similar products specific for the venoms of the various snakes native to the country.

14. *Diphtheria Antitoxin.* This product is one of the greatest achievements of applied immunology. Higher than ever in antitoxic content per given volume, more stable and freed to a larger and larger extent from non-antitoxic proteins, it remains a sovereign remedy for diphtheria. Here again early administration enhances its value. The accepted but not always practised modes of administration are intravenously in the severest cases, intramuscularly in mild and also possibly a part intravenously in moderately severe infections, but subcutaneously only for prophylaxis. From the experimental work of Schick there would appear to be no advantage in giving more than 500 units per kilo of body-weight in the severer cases, and this amount corresponds to the maximum dosage recommended by Park and the manufacturers of this product. Any hesitancy about dosage should be dispelled by decision to administer the higher amounts recommended. Any suspicion that the patient is suffering from diphtheria demands the immediate injection of antitoxin in full dose without waiting for a bacteriologic report.

The prophylactic use of diphtheria antitoxin is decreasing. It is now prefered to perform Schick tests on

persons exposed and to take nose and throat cultures. When the reaction to the Schick test and the result of cultural examination are negative the individual is released from observation; where the Schick test is negative and the culture positive the person is considered as a carrier; where the Schick test is positive and the culture negative, daily cultures and clinical examinations are made; where both the Schick test and culture are positive a dose of 1,000 units or more of antitoxin should be given.

15. *Erysipelas Antitoxin.* The facts that hemolytic streptococci are intimately concerned in this disease, that these cocci produce a toxin analogous to that elaborated by scarlatinal streptococci, and that erysipelas is essentially a toxemia, would seem to furnish a basis for antitoxic therapy. Amoss and also Birkhaug have developed such antitoxins, which are now supplied in concentrated form, and clinical reports of the results following their use are mainly favorable. The close relationship of streptococci of the erysipelas group to those of the scarlatinal group would seem to be ground enough for employing polyvalent scarlet fever streptococcus antitoxin in the treatment of erysipelas. The English follow this view as does also McCann, apparently with satisfaction. On these grounds, therefore, it might be predicted that scarlet fever streptococcus antitoxin might or might not be of benefit in erysipelatous conditions. The protection afforded is temporary and should not be expected to prevent relapses.

16. *Scarlet Fever Streptococcus Antitoxin.* The potency and the immunizing compass of this product have been increased by the addition of different toxigenic strains of scarlatinal streptococci to the antigens used for immunizing the producing horses; by improvements in the scheme of injection and by refinements in the concentration process. The methods for testing the potency still leave much to be desired, but manufacturers obviate this difficulty by recommending an amount which is usually sufficient for the case. This antitoxin given in adequate amounts early in the disease reduces the toxemia in a gratifying way, and the greater the toxemia (in early cases) the more striking the effect. Since it is essentially an antitoxin one would not anticipate that it would prevent the development of septic complications, except in so far as it, by lessening the debilitation of the patient, might raise the general level of resistance to further invasion by this streptococcus. Some authors recommend its use in all cases of scarlet fever while others would limit its use to the moderately severe and severe cases.

The prophylactic use of this antitoxin does not seem indicated unless exposed persons are to be away from daily medical observation. The disease usually attacks only about one in ten of those exposed, the antitoxin confers passive immunity for a matter of only two weeks or slightly more, while the source or sources of infection may continue to be present and cause this fever in exposed persons in whom this passive immunity has disappeared. Then second or subsequent injections of this product may be followed by serum sickness. The daily inspection

of contacts, with the immediate administration of the antitoxin at the first symptoms of scarlet fever, would in the main, seem to be the better practice.

17. *Tetanus Antitoxin.* Few biologic products have been subject to such trial as was given tetanus antitoxin during the World War. Out of that welter it was learned that a prophylactic dose of 1,500 units, administered shortly after the wound was received, would ward off tetanus if the wound were slight or required no further surgical interference. The protection was not sufficient, however, to prevent development of the infection in those cases requiring subsequent operation. It, therefore, became the rule to give antitoxin not only at the time of the wounding but before each surgical operation. This rule should hold in civil as in military life. For treatment the antitoxin should not be given grudgingly. It should be injected intraspinally at the earliest moment, and repeated frequently and in large doses. Administration by the venous route or into nerve sheaths is inferior in effect to injection into the spinal canal.

18. *Other Serums.* In addition to the serums just discussed, there is normal horse or other animal serum for the arrest of hemorrhage and the treatment of burns as well as a number of analogous products which, because their merits can not be measured according to our chosen standards need not be included here. For example, in the catalogs of foreign manufacturing establishments one finds listed such products as coli-paracoli, grippe, icterohemorrhagica, leprosy, thyroid, typhoid, uremia and vaccinia antiserums, all of which under the ruling of the United States Hygienic Laboratory would be classed as products for which no standard of potency exists.

Summary

With these theoretical considerations the clinician should neither expect nor demand that immune sera do more in controlling the diseases for which they are intended than the immunologist may honestly predict for them. Bearing in mind that serums represent proteins foreign to the human body, the prudent physician will determine the allergic condition of his patient before such treatment and be ready with epinephrine to combat any untoward reaction following serum injections. For the same reason such a physician may spare his patients the possibility of future serum sickness by not giving serums needlessly. Here, and on this account even more caution is demanded than in the use of vaccines.

Fresh and potent serums, and only those of proven value, given early in the disease and by the most favorable route, continue to be the physician's greatest and sometimes sole aid in curing some of the more malignant infectious diseases.

This critical review of serums and vaccines must be taken as of today. The development of non-specific biologic therapy, the perfection of new methods of serum and vaccine production and the discovery of other agents of this kind will necessitate new or revised appraisals. Disappointments will be fewer if general use waits upon theory, upon laboratory experiment, and upon controlled clinical observation.

The Diagnosis of Gonococcal Arthritis With Report of Three Cases in Patients With Chronic Rheumatic Endocarditis*

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NOT so many years ago the term gonococcal arthritis connoted an ankylosing monarticular process; today we know that gonococcal arthritis is usually a polyarthritis which may so closely simulate rheumatic fever as to lead to diagnostic error unless one is constantly alert to suspect and search for the evidences of gonococcal infection.

We have also learned that all prostatitis is not gonococcal nor need it have even started as such, and we have gained a hearty respect for both venereal and non-venereal prostatitis as a focal cause of such distant troubles as arthritis, iritis and neuritis.

Notwithstanding these advances, it seems to me we are still far from appreciating both the frequency with which neisserian infection is responsible for arthritic phenomena and the difficulties of recognizing this factor when it occurs.

Impressed with this view, we have attempted for the past few years to make sure that the possibility of gonococcal infection was carefully investigated in every patient with acute or chronic arthritis, including even apparently typical rheumatic fever, admitted to the adult medical service at the Hospital of the University of Pennsylvania. As always happens when such a state of mental "sensitization" exists, more instances of the disease in question were discovered. After careful investigation a number of cases of supposed rheumatic fever proved to be gonococcal arthritis and among the infectious arthritis group a greater percentage were attributed to gonococcal infection. For example, during 1928, among 46 cases of arthritis there were 20 in which investigation supported an initial suspicion of gonococcal etiology, and further study resulted in 14 of these 20 being finally so diagnosed. I have no desire to present any statistics but merely to report some of our experiences and conclusions.

At the start let me emphasize the difficulties inherent to the making of the diagnosis of the gonococcal nature of an arthritis. Only when an acute arthritis develops during acute gonorrhoea can one safely and easily make this diagnosis. Under other circumstances, it is usually made with difficulty and doubt. Even the discovery of a gonococcal infection does not prove its causal relation to an existing

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arthritis any more than does the finding of a peridental abscess. Furthermore, the tendency of the gonococcus to die out and leave only a secondary flora as evidence of a former gonorrhoea in both males and females adds to the difficulty.

The uncertainty is in a large measure due to the fact that all the diagnostic criteria which can be routinely used are far from satisfactory. They include the history, the character of the arthritis, other clinical features, the complement fixation test, roentgenology, joint puncture, the course of the disease and the results of treatment. Let us briefly discuss each of these.

History. Both the previous medical history and the circumstances immediately preceding the onset of the arthritis are important and yet may be very deceiving. When a clear story of gonorrhoea is obtained it must obviously arouse suspicions that a subsequent arthritis may be gonococcal, even though a story of joint injury is obtained. Frequently injury seems to determine the onset and the localization of a gonococcal arthritis. A negative history on this point is to be given no weight at all not only because venereal disease is often denied but because in the female its presence is often unknown. Far more significant in the female is the history of leucorrhoea, pelvic inflammatory troubles or some chronological relation of arthritis to marriage or to child bearing.

Among our recent cases are examples of each of these relationships; in one man three of five attacks of gonorrhoea were followed by arthritis. It is the rule that if gonococcal arthritis is to occur in an individual it will usually appear with the first gonorrhoea and having once occurred will recur with each fresh gonorrhoea. In another, the entire sequence of gonorrhoea, polyarthritic stage, monarthritis in sternoclavicular joint, and finally the typical painful heel of the os calcis spur could be elicited.

The patient's age at the onset of the arthritis must be given some weight; a very youthful onset, of course, argues against an arthritis being neisserian unless the case belongs in the fortunately rare infantile group. There is no question but that such cases do occur and Cooperman[1] has reported an epidemic with 44 such cases of gonococcal arthritis all in infants from the same hospital ward. Apparently infants readily develop gonococcal arthritis from very slight local lesions.

There may be no age above which a primary attack of rheumatic fever may not occur but a primary attack certainly becomes less common after the age of twenty. Similarly, the presence or absence of tonsillitis, growing pains, chorea or rheumatic heart disease would seem to be of importance in the history. This question will be referred to later and several cases reported to illustrate the difficulties.

It has usually been agreed that gonococcal arthritis is far more common in males than in females. Thomas[2] had 97 males and but 10 females in his recently reported series but it is doubtful whether this expresses the true proportions. The recognition of

[1]Cooperman, M.B.: Am. J. Dis. Child., 1927, 33, 932.

[2]Thomas, B. A.: J. Am. Med. Assn., 1927, 89, 2147.

chronic gonorrhoea is far more difficult in the female and the history far less helpful as a rule. In our recent cases, there were as many females as males.

Character of the Arthritis. Emphasis was first placed on the monarticular feature of neisserian arthritis; next on the tendency of the polyarthritis involvement to subside in all but one large joint, often the knee. Just as long as this criterion was demanded for the diagnosis of gonorrhoeal arthritis only such cases as exhibited these features were recognized as such and so diagnosed. Today it is accepted that the temporomandibular and sterno-clavicular joints are often involved in gonococcal arthritis, seldom if ever in rheumatic fever. Blake[3] in the best available article on gonococcal arthritis supports this view. Among our recent cases of neisserian arthritis, there were instances of involvement of each of these two joints while neither joint was involved in the non-gonorrhoeal group.

Nevertheless one cannot usually distinguish on the basis of the arthritic picture some instances of so-called neisserian arthritis from rheumatic fever; nor others from non-gonorrhoeal infectious arthritis. There is not enough difference in the onset, the order of involvement, the number of joints involved, those involved, the duration of individual joint involvement nor in the severity of the local symptoms to permit one to make a satisfactory differential diagnosis.

The phrase 'so-called neisserian arthritis' was used above with a purpose. It is possible that we are trying to merge under this term two distinct forms of arthritis; one more acute and specifically due to the gonococcus often with that organism in the joint, the other arising no less from a focus containing gonococci but reacting to this focal infection in a non-specific manner. In the second type, although gonococci might be found in the focus there would also be a free flora of secondary invaders. In this form gonococci would not be present in the affected joints and the process would be chronic and not differentiable from a non-gonococcic infectious arthritis arising from a staphylococcic or streptococcic focus in tonsil or sinus. Strictly speaking these cases should not be termed gonococcic even though the initial infection was gonococcal and even though gonococci may still persist in the focus at the time of development of the chronic infectious arthritis.

In other words, even the finding of gonococci in what seems to be the causal focus of infection certainly does not prove that the arthritis, although due to that focus, is truly gonococcal. If we accept this view, it would explain many of our difficulties—the variations in the arthritic process, in the radiologic findings, in complement fixation of cases which we now attempt to include in one diagnostic group.

Other Clinical Features. Some authorities have stated that there are differences in the height of fever and its duration, in the sweating, in the leucocytosis or in the anemia. None of these criteria have seemed helpful to me.

Endocarditis is another matter and

[3]Blake, F. G.: in Blumer's Bedside Diagnosis, Saunders, 1928.

its appearance during or soon after an arthritis argues strongly for a rheumatic process. Simple infectious arthritis seldom if ever has a cardiac complication while the rare instance of gonococcal endocarditis soon forces its diagnosis upon the physician. The same reasoning applies to pericarditis and even to myocarditis and disturbances of rhythm. One of our cases of arthritis strongly suspected of being neisserian developed a paroxysm of auricular fibrillation thus raising the interesting question as to how far this favored a diagnosis of rheumatic fever.

The leucocyte picture deserves mention. The leucocytosis will be high in acute purulent monarticular gonococcal arthritis but as a rule the leucocytosis will be greater in rheumatic fever than in polyarthritic neisserian arthritis. There is no difference in the range of the total white cell count between infectious non-gonococcal arthritis and gonococcal polyarthritis; nor do I give any weight to the claim that gonococcal infections are to be recognized by the occurrence of an eosinophilia. It is true that gonococcal pus often contains many eosinophils and it is probably from this that a circulating eosinophilia has been erroneously assumed. In none of our recent cases has there been an eosinophilia of more than 2 per cent, except one count which was 6 per cent of a normal total.

Complement Fixation. It seems to be generally accepted that a negative reaction does not exclude the presence of a gonococcus infection, but that a positive test is certainly of value. Kolmer[5] claims that gonococcal arthritis yields from 80 to 100 per cent of positive reactions. During the past year in the cases of what we concluded were neisserian arthritis the complement fixation was positive in a little less than half. Among the negative cases were 3 in which gonococci were actually found; all of these negative cases were of long enough duration for a complement fixation test to have developed. The reaction does not become positive for a month and often not for six to eight weeks—a point not to be forgotten. One of the positive tests may have been due to vaccine given at a previous hospital, a possibility which also must never be forgotten.

Roentgenologic Evidence. The X-ray Department of the University Hospital, under Dr. H. K. Pancoast, recognizes two distinct joint pictures produced by gonococcal infection; the one is a chronic deforming arthritis with both hypertrophic and atrophic changes and is not to be differentiated as to cause from the roentgenogram alone. This corresponds to the nonspecific form already referred to. Sometimes the presence of a spur on the os calcis will arouse suspicion. Baetjer especially emphasizes that long spurs are probably of gonococcal etiology.

The other form is an acute destructive process analogous to that produced by streptococci or pneumococci but a little less rapid. This picture occurring in a case lacking the history of a serious streptococcic or pneumococcic

[4]Mondor and Urbain: Comptes rend. Soc. de Biol., 1927, 96, 513 et al.

[5]Practical Text Book of Infection, etc., Saunders, 1923.

infection is strongly suggestive of a gonococcic etiology.

Perhaps intermediate between these two is a rarer picture in which punched out areas occur in the bone underlying localized areas of involved cartilage; this resembles the picture seen in gout.

Among 14 possibly neisserian cases, the X-ray supported the diagnosis in 8; of the other 6 one was a proved case of gonococcic infection but the X-ray was taken only 17 days after onset, far too soon to show any change; a second proved case had only synovitis; two were quite sure cases and might have been expected to exhibit suggestive changes but even on review did not; the other two were our least sure cases and the X-ray failure to assist added to our uncertainty.

Reviewing these films brought out that much can often be learned by repeating the X-ray study after an interval of several weeks. The progress of the process was in several instances an important aid in diagnosis.

While it is perhaps true as Baetjer and Waters[6] write that gonococcal arthritis does not present a distinct X-ray appearance, yet our experience would suggest that with the aid of a judicious use of the history the X-ray may be of valuable diagnostic assistance. Especially is this true if we distinguish between acute truly gonococcal arthritis and the other more chronic not strictly gonococcal process.

Joint Puncture. Our experience adds nothing to accepted views on this point. If the process be acute a cloudy fluid will be obtained which on staining will reveal many neutrophiles. Gonococci will usually not be found in the fluid; therefore one should search in the synovial membrane, taking a piece for biopsy.[7] When Gram negative diplococci, often intracellular, are found in stained spreads from an infected joint the organism is assumed to be the gonococcus. In the vast majority of instances this assumption is justified but it must not be forgotten that a monarthritis often of the knee, is not an uncommon complication of meningococcus infection and further that meningococcus bacteriemia occurs with little or no meningitis and finally that the meningococcus is a Gram negative diplococcus often intracellular and indistinguishable from the gonococcus by any staining method. There should be no opportunity for confusion in cultures. As an alternative to joint puncture a neighboring lymph node may perhaps be cultured. Forkner[8] successfully cultured gonococci from a lymph node from the axilla of a patient with a typical chronic infectious arthritis.

Axhausen[9] has recently pointed out that not all acute monarticular arthritis giving the picture of gonococcic arthritis is due to the gonococcus.

Course of Disease and Results of Treatment. Attempts to draw diagnostic aid from the course of an arthritis have been unsuccessful with us. It is commonly accepted that the patient with rheumatic fever obtains more relief from salicylates than does

[6]Injuries and Diseases of the Bones and Joints: Hoeber, New York, 1927.

[7]Plisson, L.: Le Prog. Med., 1927, 42, 1543.

[8]Forkner, C. E.; Bull. Johns Hopkins Hosp., 1928, 43, 257.

[9]Klinische Wochenschrift, 1927, 6, 732.

one with gonorrhoeal arthritis. This is in a measure true but it is hard to use this as a diagnostic criterion. Gonococcal polyarthritis may leave behind it just as little disability as does rheumatic fever but when gonococcal arthritis lingers in the knee or other large joint, ankylosis often results. Rheumatic fever does not produce ankylosis but acute infectious arthritis of any type may.

Case Reports. Each of the three cases to be briefly described presents gonococcal arthritis in a patient with an old rheumatic endocarditis. This coincidence raises some interesting questions. At first glance it would seem that evidence of a former rheumatic infection would argue that a subsequent polyarthritis would also be rheumatic. Such evidence might consist of a clear history of rheumatic fever in childhood, of repeated tonsillitis or chorea, or the discovery of a residual rheumatic endocarditis. Undoubtedly, as Torrey[10] has emphasized, an adult is far more liable to rheumatic fever if during childhood a previous attack of rheumatic fever has occurred. May it not be, however, that the same adult is rendered by the earlier rheumatic fever more liable to other joint affections as well as to further rheumatic fever? Blumer[11] has an editorial footnote on this point suggesting that a previous rheumatic fever makes the individual more subject to gonorrhoeal arthritis. The following cases suggest that this is so.

CASE I. M.H. (1928-1147). A white, unmarried female aged 22 developed three months before admission, pain and swelling in the right elbow and knee. The knee recovered in one day, the elbow persisted; there was fever for two weeks.

After three months there was swelling and ankylosis of the right elbow and also limitation of motion in shoulder with considerable atrophy. Some involvement but to a less degree of the right wrist and hand. No other joints affected. The interne's tentative diagnosis was gonorrhoeal arthritis. Confirmatory evidence was obtained by the finding of gonococci in the vaginal discharge and by Dr. Pancoast's report that the roentgenologic appearance of the right elbow was strongly suggestive of gonorrhoeal arthritis.

Another side of the case, however, was presented by the finding of an undoubted mitral stenosis and of foci of infection in the tonsils, sinuses and mastoids. The mitral stenosis was in all probability an evidence of chronic rheumatic endocarditis even in the absence of any history of rheumatic fever or chorea.

Under thorough treatment all but the ankylosis improved and the case was sent for an arthroplasty.

CASE II. M.B. (1928-879) a white married woman of 24 years of age was admitted with pain in the right elbow which had been present for one month. No other joints affected at the time but two years previously a sharp attack of polyarthritis.

The items suggesting a possible neisserian basis for the arthritis included a former salpingitis requiring operation, the presence of endocervicitis even though no gonococci were found, a strongly positive complement fixation and a roentgenologic suggestion of gonococcal arthritis.

On the other hand, the heart was enlarged to the left and a double murmur at the apex testified to mitral valvulitis with both stenosis and regurgitation. There was no history of any former rheumatic fever, chorea, or tonsillitis.

Nevertheless here again, we felt justified in the diagnosis of chronic rheumatic endocarditis and acute neisserian arthritis.

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[10]Torrey, R. G.: Tice's System of Medicine.

[11]Blumer, G.: Bedside Diagnosis, Volume 1, p. 32, Saunders, 1928.

CASE III. W.B. (1928-894) a divorced white male of 28 years of age had at 21 years his first attack of polyarthritis. During the following six years, he suffered six similar attacks each lasting from 3 to 6 months and involving an increasing number of joints. The attacks are worse in the winter.

In his earlier history there is no mention of rheumatic fever, chorea or tonsillitis. He admits gonorrhoea at 23; two years after his first joint attack.

On admission, the pain and stiffness involved the shoulders, knees, hips, sacro-iliacs, both mandibular joints and the left sterno-clavicular. Physical examination revealed evidences of both aortitic and mitral valvulitis—presumably rheumatic in nature. The Wassermann was negative. The prostate was heavily infected but no gonococci were found. No suspicion of gonococcal arthritis was supplied by the X-ray. The complement fixation was positive, but this may have been due to vaccine given in a previous hospital.

In this case one must admit the old gonorrhoea and the persistent prostatitis but these do not prove the gonococcal nature of the arthritis. However, the involvement of the sterno-clavicular and temporo-mandibular joints would be adduced by some as suggesting a neisserian process.

All of these patients have been followed sufficiently long to exclude all reasonable possibility of the cardiac lesions being gonococcal in nature nor did they present in the hospital the evidence of this infection. It was formerly thought by some that gonococcal arthritis was often associated with a gonococcal infection of the heart, which often was mild and recovered. This is no longer believed. According to our present views the above three cases are unquestionably instances of rheumatic heart disease. The absence of earlier rheumatic arthritis is interesting in that in its absence the joints would perhaps not have been expected to be peculiarly susceptible to later gonococcal arthritis.

Summary. 1. Gonococcal arthritis is a frequent disease in both males and females.

2. It is protean in its manifestations and may closely stimulate rheumatic fever.

3. The true nature of a gonococcal arthritis will often be overlooked unless this etiologic possibility is kept constantly in mind.

4. Diagnosis of this condition is often difficult; the diagnostic methods unsatisfactory when used singly; combined they will usually prove sufficient.

5. It is suggested that a gonococcal focal infection may cause either a specific gonococcal arthritis or a non-specific infectious arthritis. Many of our diagnostic difficulties may arise from this.

6. There is some reason to believe that rheumatic infection prepares the soil not only for recurrences of rheumatic fever but also for other types of arthritis including the gonococcal.

Complications and Sequelae of Chronic Ulcerative Colitis*

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EVERY serious disease entails dangerous consequences, either during the progress of the illness or as a result of nature's effort to restore destroyed tissue. Particularly is this true of severe chronic infections. In the healing of tuberculosis, formation of the scar may result in serious loss of function. Pneumonia, through the sequel of empyema, not infrequently results in marked deformity of the chest. Another disease, hitherto thought of as a serious infection of the colon, has usually been considered without particular reference to its associated complications. There are few diseases more annoying or more severe in their course than chronic ulcerative colitis and, further, the conditions which this infection leaves in its wake are among the most distressing encountered in the practice of medicine. The conditions following, or closely associated with, chronic ulcerative colitis are multiple.

In a series of 693 cases of chronic ulcerative colitis examined at The Mayo Clinic in the five and a half years from January 1, 1923, to July 1, 1928, various significant complications and lesions closely associated with the disease occurred as sequelae to or during the course of the infection. There were sixty-nine cases of polyposis of the colon, fifty-nine cases of stricture of the rectum or colon, thirty cases of arthritis, twenty-six cases of perirectal abscess, seventeen cases of cutaneous lesions, eight cases of nephrosis, or nephritis, seven cases of endocarditis, seven cases of splenomegaly, eighteen cases of perforation of the colon, fifteen cases of malignant disease, five cases of ocular disease, three cases of fatal hemorrhage, two cases of renal calculi, and one case of mesenteric thrombosis, and one case of tetany

It must not be thought that each of the foregoing complications occurred in individual patients. Frequently multiple complications occurred in one case. One patient had with the colitis, endocarditis, arthritis, erythema nodosum, and iritis. The three conditions, chronic ulcerative colitis, arthritis and erythema nodosum, occurred together in several patients. Chronic ulcerative colitis, perirectal abscess and iritis occurred together. Perirectal abscess, polyposis and malignant disease occurred with chronic ulcerative colitis several times. Many other in-

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TABULATION
DISTRIBUTION OF 268 COMPLICATIONS OCCURRING IN 693 CASES OF CHRONIC ULCERATIVE COLITIS

Complication	Cases in which complications occurred	Per cent
Polyposis	69	10.0
Stricture	59	8.5
Arthritis	30	4.33
Perirectal abscess	26	3.7
Skin lesions	17	2.45
Renal insufficiency	8	1.15
Endocarditis	7	1.0
Splenomegaly	7	1.0
Perforation	18	2.6
Malignant disease	15	2.16
Ocular disease	5	0.7
Hemorrhage (fatal)	3	0.4
Renal calculi	2	0.2
Mesenteric thrombosis	1	0.15
Tetany	1	0.15

stances of associated lesions could be mentioned. The fact should be stressed that complications do not preclude recovery from chronic ulcerative colitis.

In this series of cases multiple polyposis (fig. 1) occurred as the most common complication. In a series of 117 cases studied by Logan in 1919 there were polyps in nineteen, and in a later series studied, polyps occurred in twenty-six of 200 cases. Just as the disease, chronic ulcerative colitis, usually begins in the rectum, so it is the most common site of origin of polyps. Later the number increases as they appear in the more proximal portions of the colon. That they originate during the progress of the disease has been repeatedly demonstrated. In the earlier stages of the disease, the inflammatory phases so accurately described by Buie are seen. With the appearance of the larger ulcers, between which are left islets of mucosa, there is a certain heaping up of mucosa and apparent pinching off at the base so that two types of polyps may be differentiated easily: (1) a plateau-like excrescence appearing as definite mucosal hyperplasia, and (2) large pedunculated polyps which on section are found to be adenomatous polyps. If both of these occur extensively and are large enough to visualize by roentgenogram by barium enema, the prognosis may be grave. On the other hand, if limited to the field of the proctoscope they may be fulgurated and their potential danger becomes minimal.

Rectal stricture is the second most common sequel of chronic ulcerative colitis. In discussing stricture in this disease the reference is not to the ordinary narrowing of the colon which usually occurs after one or more attacks of ulcerative colitis. Interest is directed, rather, to localized regions of inflammatory and scar tissue which interfere materially with the passage

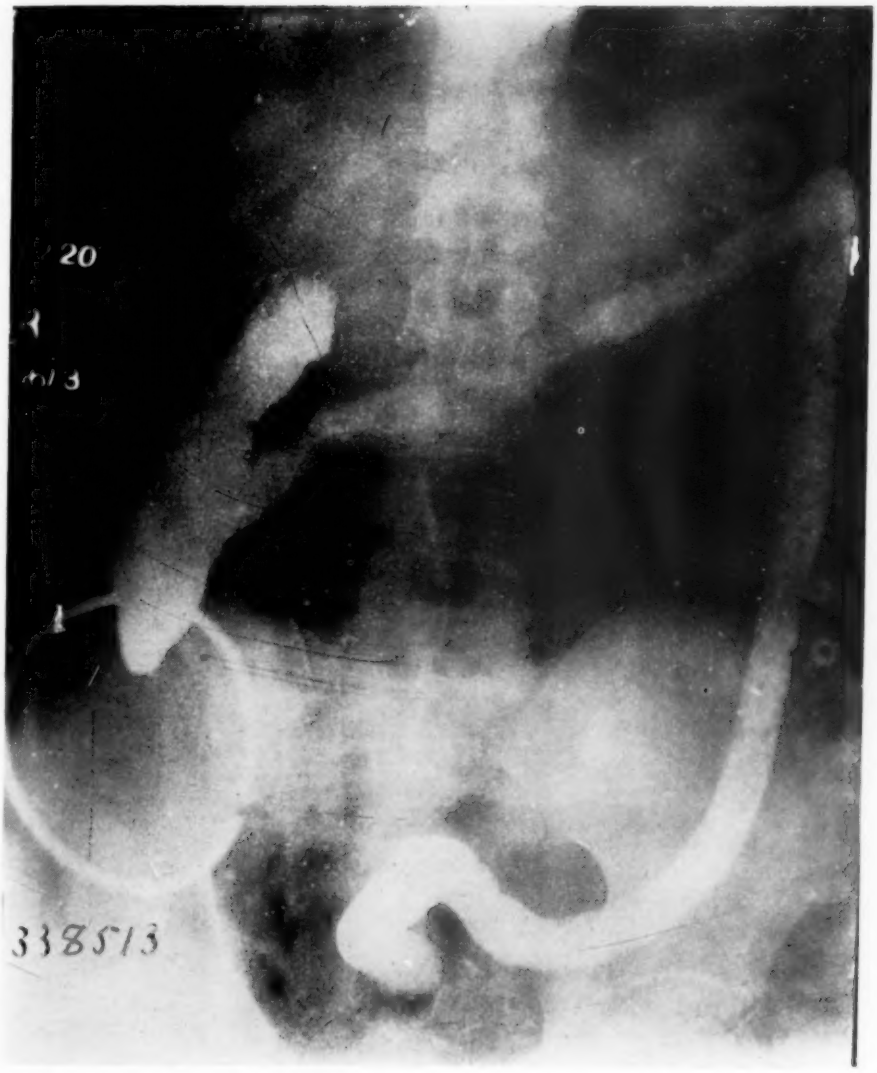

Fig. 1. Colon after barium enema in a case of chronic ulcerative colitis and multiple polyposis.

of the normal fecal current, thus inhibiting normal rectal function. In this series there were cases of multiple stricture in some of which the lumen was so narrow that pockets of pus would accumulate proximal to the stricture in various parts of the colon (fig. 2). The commonest type of stricture, however, is a localized narrowing of the rectum on a diffusely narrowed base. These strictures are organic constrictions of the bowel to diameters as narrow as 0.5 to 1.5 cm., measured proctoscopically. The decrease in the relative number of such strictures as a complication is striking; in the years 1923 and 1924 stricture developed in 19 per cent of cases and in the next three and a half years, in only 6.3 per cent, a reduction by approximately 66 per cent. This can be attributed in part to newer methods of treatment.

Whether or not arthritis should be called a complication or an associated disease is a debatable question, but from the clinical standpoint it is generally considered to be a complication. In a large series of patients with chronic ulcerative colitis and arthritis in whom the diplostreptococcus of chronic ulcerative colitis was isolated from rectal lesions and injected intravenously into animals, the lesions which resulted in animals were, as far as the rectum was concerned, in all essentials like the rectal lesions of patients; associated lesions in the joints, however, never have been noted in the animals. On the other hand, in a careful analysis of the histories of patients afflicted with chronic ulcerative colitis and infectious arthritis, various types of cases are noted: (1) those in which each exacerbation of colitis is followed by a recurrence of the arthritis and in which, with improvement of the colitis, there is associated relief from the arthritis; (2) those in which the attack of arthritis may precede the colitis, and (3) those in which both disturbances occur in the same patient, apparently without relation. A further study of these cases is under way.

Perirectal abscess (fig. 3) is one of the more serious, although fortunately uncommon, complications. Either one of the anal crypts becomes infected from the constant purulent rectal discharge or deep ulcers burrow beneath or to the side of the anal sphincters and point as one or multiple perirectal abscesses. From these abscesses, frequently, a pure culture of the diplostreptococcus of chronic ulcerative colitis is recovered. Conservative treatment in these cases cannot be urged too strongly. That there be the least possible surgical interference is most important. If the usual radical incision and drainage is carried out, most unfortunate perianal spreading of infection and functional anal deformity may result.

Perforation of the colon (figs. 4 and 5) is another extremely serious condition which occurs in the more extensive and severe cases of chronic ulcerative colitis. Its incidence has been discussed elsewhere[3].

Any discussion of an inflammatory disease of the colon would seem incomplete without reference to the lesions that occur in the skin. In this series these lesions included erythema nodosum, erythema induratum, chronic eczema, eczematoid and vegetative dermatitis, hemorrhagic purpura, ir-

Fig. 2. Colon with multiple strictures after barium enema and after belladonna had been administered.

Fig. 3. Multiple perirectal abscesses that had ruptured or had been incised, causing severe rectal deformity in a case of chronic ulcerative colitis.

Fig. 4. Colon with multiple perforations and chronic ulcerative colitis.

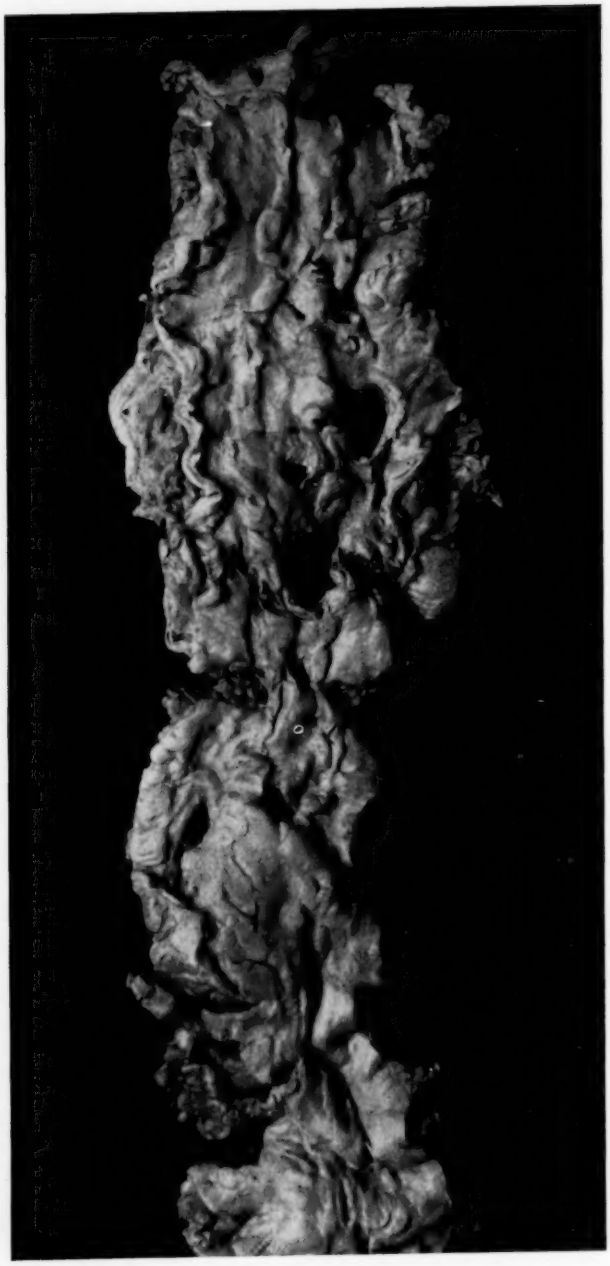

Fig. 5. Part of the colon shown in figure 4.

regular ulcers of the leg, pityriasis rosea, neurodermatitis, erysipelas, pellagra and pemphigus. There may not be any close relationship between the colitis and most of these, but an interesting clinical observation is the fact that with relief from the colitis, a goodly number of them clear up. The repeated concurrence of erythema nodosum, arthritis and colitis is worthy of comment.

Malignant disease as reported previously[1] is usually of rapid, early fatal type, frequently occurring as multiple carcinoma of a high grade of malignancy in the colons of young persons and in association with polyposis.

Renal insufficiency as a complication of severe dysfunction of the colon is serious. Demonstrable renal injury has occurred only rarely in this series of cases of chronic ulcerative colitis. Evidence of such impairment has included albuminuria, hematuria, edema, increased blood urea, and elevation of blood pressure, as well as changes in the ocular fundi.

Endocarditis occurred rarely with or as a sequel to chronic ulcerative colitis. It appeared in only 1 per cent of the cases, and only once could the fatal termination of the disease be attributed to this condition. Growth was not obtained on blood culture; nevertheless, in a few other cases, in which endocarditis was not a factor, but in which chronic ulcerative colitis was severe, the diplostreptococcus of chronic ulcerative colitis was isolated by blood culture.

In seven of the 693 cases there was unusual splenomegaly. Several of these patients had enormous spleens. All but one occurred in young persons; the ages of the patients were fifty-one, forty-two, thirty, twenty-three, twenty, fifteen and seven years. In the patient aged fifty-one years Banti's disease and biliary cirrhosis were diagnosed; in all the others, infectious splenomegaly was considered. In the case of the boy aged fifteen years, there was associated juvenile hepatic cirrhosis, so diagnosed at necropsy, and in two cases there was associated purpura hemorrhagica.

Ocular disease, although it occurred in only five cases in this series, was definitely a complication, usually in the form of iritis or uveitis. In all cases it occurred in the presence of one or more other complications; that is, perirectal abscess, endocarditis, arthritis, and erythema nodosum. This adds evidence to the theory of the blood-borne nature of these infections. Crohn[5] has reported several similar cases.

That fatal hemorrhage from the colon does not occur more frequently is rather astonishing when the extensively ulcerated surface present in these cases is considered.

Renal calculi are mentioned here because clinical symptoms of their presence occurred during the course of the disease.

Mesenteric thrombosis played a part in the fatal outcome in one case.

Tetany occurred in only one case in which colectomy was performed and in which there were multiple operations on the ileum for obstruction. The rarity of this symptom is striking when the terrific intractable diarrhea with which so many of these patients are afflicted is considered.

In addition to these closely associated pathologic lesions, other condi-

tions which occur in the course of chronic ulcerative colitis should be mentioned. A peculiar mental attitude develops in many cases and in twenty-five of this series there were symptoms of neurologic phenomena. Seventeen patients failed to respond to treatment and the colitis progressed toward its terminal events. Twelve other patients had duodenal ulcer; ten had ulceration involving parts of the colon, producing conditions that simulated filling defects; there were five cases of pregnancy during the course of the disease in which symptoms improved or completely disappeared during the pregnancy; in four cases lymphosarcoma occurred in the colon; there were two cases of lymphatic leukemia, and one case of pericolic lipomatosis.

It should also be noted that there were four cases in which various types of abdominal surgical procedures precipitated acute attacks of ulcerative colitis which proved fatal to the patients.

There were only five instances in which the disease occurred in more than one member of a family. Those affected in groups were two sisters, two brothers, a father and his daughter, and in two instances a mother and her son. Such an incidence could occur readily in any infection and would argue against the idea that the disease might be contagious.

Report of Cases

Case 1, polyposis.—A man aged twenty, was admitted to The Mayo Clinic September 26, 1925, with a history of bloody dysentery of nineteen months' duration and with a maximum of thirty to forty stools in twenty-four hours. He stated that his condition had been as bad as this for at least 100 days in succession. A diagnosis of amebic dysentery had been made elsewhere, although amebae had not been found in the stools.

The patient was acutely ill with a maximal temperature of 102°, and he had many rectal discharges containing pus and blood. He suffered from incontinence of the rectum and had lost 24 pounds in weight. The pulse rate was 90 and the blood pressure 120 systolic and 90 diastolic. The abdomen was moderately tender. At proctoscopic examination, September 28, 1925, there were noted a diffuse granular involvement of the rectal and sigmoidal mucosa, associated edema, a hemorrhagic tendency, and scattered punched-out ulcers. The diagnosis was chronic ulcerative colitis. During the next five months his condition varied. Improvement was slow but by October 24, 1925, his condition had progressed so that he was dismissed.

The patient returned in February, 1926, much worse than on first admission, reporting steady failure during the month. On the report of proctoscopic examination made February 23, it was noted that there were large, sloughing, ragged, undermining ulcers of the rectum with bridging of the mucosa between large ulcers, a very serious condition. Ileostomy as an emergency was suggested, but because of the severity of the condition the idea was abandoned. Treatment then consisted of tincture of iodine given by mouth, large doses of kaolin alternating with bismuth, opium and paregoric, and small doses of vaccine prepared from the diplostreptococcus which was isolated practically in pure culture from the ulcers in the rectum on both occasions. He slowly began to improve and after several months was able to go home.

September 22, 1926, the patient stated that he had gained 37 pounds in weight in the preceding four months; he was having six to seven movements of the bowel in twenty-four hours with only occasionally a little blood and mucus. The proctologist reported the mucosa practically normal. There were a few pitted scars scattered over a slightly pale mucosa and multiple polyps from 0.3 to 0.7 mm. wide and from 0.3 to 1.5 cm. long; some bled easily. The

diagnosis was polyposis following healing of extremely advanced chronic ulcerative colitis. Clinically the patient was in excellent condition. He was dismissed with instructions to take vaccine subcutaneously. May 23, 1927, he returned, clinically well, stating that he had had the best winter since the beginning of the illness. He had gained 50 pounds in weight and and looked the picture of health. There had been an average of three bowel movements daily for months and blood had not been seen in the stools for at least a month. At this time the proctologist reported healed chronic ulcerative colitis, leaving polypoid areas and polyps. Some small polyps seen January 23, 1927, had disappeared. The mucosa between polyps was normal except for the scars of the infection. A series of fulgurations of the rectal polyps was carried out without incident. The patient was free of symptoms then, but because of the inability to fulgurate all the polyps he returned in December, 1927. At this time it was noted on proctoscopic examination that there were still several polyps in the rectum but that the mucosa was healthy. The remaining polyps were fulgurated.

August 9, 1928, the proctologist noted some scars in the rectum but no ulceration. The lumen was practically normal in diameter. The areas fulgurated did not show polyps.

Case 2, stricture.—A man aged thirty-three years came to the clinic in December, 1928, with a history of bloody dysentery of ten years' duration, accompanied by ten to fifteen bowel movements daily.

The patient was emaciated and in the last few months prior to coming to the clinic he had lost 19 pounds. Proctoscopic examination revealed chronic ulcerative colitis, a definite annular stricture 13 mm. in diameter situated 2 cm. above the pectinate line, and the whole rectum contracted to two-thirds its normal size. The roentgenogram showed involvement of the entire colon. The Wassermann reaction on the blood was negative. Stool examination was negative for acid-fast bacilli, parasites, and ova. Analysis of gastric content gave a total quantity of 110 c.c., total acidity of 40 and free hydrochloric acid of 18. The blood count was essentially normal, except that leukocytes numbered 10,800 in each cubic millimeter. The tonsils were septic and there was periapical infection of one tooth; these foci were removed and vaccine was given subcutaneously.

The patient returned in March, 1928, averaging three to five bowel movements daily and feeling well. At this time the proctoscope revealed activity, graded 1 on a basis of 1 to 4, with contraction of the rectum to about half its normal diameter, and the stricture admitting a large proctoscope. The patient had performed his usual business duties in the previous six months, was on the road all the time and drove his car most of the time.

Case 3, arthritis.—A man aged forty-six years came to the clinic in October, 1925, complaining of pains in the joints of one and a half years' duration. There was a history of bloody rectal discharges for three weeks. Pains in the joints of both feet had begun a year and a half before admission. Six months later some infected teeth had been extracted and the pain had left the joints but had returned four weeks later. Then it had shifted to the neck, right shoulder, arm and wrist. At the time of admission it involved one wrist and the knees. Tonsillectomy had been performed without relief, three months previously.

On admission the patient's temperature was 99.2° at 8:30 a. m. and the pulse rate was 100. He had some definite stiffness of the neck and back. The right wrist was swollen and numerous joints were stiff. October 10, 1925, the hemoglobin was 75 per cent, erythrocytes numbered 4,760,000 and leukocytes 8,700 in each cubic millimeter. The Wassermann reaction on the blood was negative. Roentgen-ray examinations of the teeth, neck, wrist, knees, chest and colon gave negative results. The proctoscopic examination revealed chronic ulcerative colitis for 24 cm., graded 2+. He was given prostatic massage because of nonspecific prostatitis, graded 3.

During a period of observation for twenty days after admission the bowel movements were ten to twelve in twenty-four hours,

all mixed with blood. In the third week of his stay the patient received a vaccine filtrate made from the diplococcus which was isolated from the lesions in the rectum. Improvement was marked and two months after admission the bowel movements were reduced to one or two in twenty-four hours. For the arthritis he was given baking and massage. He was dismissed December 16. The bowel apparently was in excellent condition; the arthritis had not improved.

The patient returned home; the arthritis improved progressively and he returned to work. In April, 1926, arthritis returned and for a month he was partially incapacitated because of swollen and sore joints. About the middle of June iritis developed, first in the left eye and then in the right. Four days after the onset he had an acute exacerbation of bowel trouble with ten to fifteen stools in twenty-four hours; the stools contained blood, pus and mucus and there was much cramping, tenesmus and extreme soreness in the lower part of the abdomen. This continued until he returned August 10, 1926.

A roentgenogram at this time showed chronic ulcerative colitis of the left half of the colon. Hemoglobin was 64 per cent; erythrocytes numbered 4,270,000 and leukocytes 5,600 in each cubic millimeter of blood. Of the leukocytes, 53 per cent were polymorphonuclear neutrophiles. Parasites or ova were not found in the stools and smears from the rectal ulcers did not contain acid-fast bacilli. Treatment with vaccine filtrate administered subcutaneously and with baking and massage was resumed August 16 and by September 24 the bowel movements were reduced to two stools daily, the patient had gained 17 pounds in weight, the rheumatism had improved and from every standpoint he was better. He was dismissed and continued to take vaccine at home for the chronic ulcerative colitis. He stated that as long as he took the vaccine he remained well.

In the first part of January, 1927, trouble returned with ten to twelve blood-streaked stools, and coincident with the recurrence of colitis was an acute flare-up of arthritis. The patient wrote for more vaccine and after taking it a month said that all his symptoms again had subsided. However, a month before his return on April 11, 1927, symptoms recurred. On admission he made the statement that when he did not have colitis, he did not have arthritis, and that with an upset of the bowels, the arthritis recurred. The treatment formerly given was resumed and two weeks after its institution he again was dismissed very much improved; he was passing only two stools a day and the symptoms of arthritis were very mild.

The next admission was June 13, 1928. At this time the colitis had recurred with twelve to fifteen bloody stools a day but without an exacerbation of arthritis. During the patient's last period in the hospital he was given the concentrated chronic ulcerative colitis serum, described elsewhere,[2] and since his dismissal, August 24, 1928, he has improved steadily.

The interesting point in this case is the apparent close relation between the arthritis and the colitis, without any other apparent or demonstrable focus.

Case 4, perirectal abscess.—A man aged fifty-eight years came to the clinic May 27, 1927, with a history of bloody diarrhea of one year's duration. He had been in hospital elsewhere for five weeks and stated that daily examinations of the stool had not revealed parasites or ova. In spite of this he was given intensive treatment for amebic infection.

On admission he was having about one stool every hour of the twenty-four, with blood, mucus and pus. His weight was 152 pounds. Hemoglobin was 64 per cent, erythrocytes numbered 3,860,000 and leukocytes 7,800 in a cubic millimeter of blood. Of the leukocytes 80 per cent were polymorphonuclear neutrophiles. The Wassermann reaction on the blood was negative. Three examinations of the stool were negative for parasites, ova and acid-fast bacilli. The tonsils were infected and two dental roots had periapical infection. The proctoscopic examination revealed chronic ulcerative colitis, graded about 2. The diplostreptococcus of chronic ulcerative colitis was isolated from the rectal ulcers and the pa-

tient was given vaccine subcutaneously. By June 18, he had made definite improvement; he had gained some weight, and stools had been reduced to nine in twenty-four hours. He was dismissed and was advised to continue the vaccine. His improvement was steady until the middle of November, 1927. During his stay at home two abscessed teeth were removed. Nine days before readmission December 20 he had pain around the anus, due to what he thought was a boil on one side of the rectum. This was lanced before his return to the clinic and at least 180 c.c. of pus was drained from it. Thereafter the perirectal pain had been very severe. On admission he had an acute exacerbation of chronic ulcerative colitis with a huge, severe perirectal abscess. The temperature was 102.5°. The hemoglobin was 58 per cent; erythrocytes numbered 3,360,000 and leukocytes 12,100 in each cubic millimeter of blood. Sixty per cent of the leukocytes were polymorphonuclear neutrophiles. Continuous hot dressings were applied to the rectum. December 22, a large perirectal abscess was drained and the culture obtained revealed the diplostreptococcus of chronic ulcerative colitis. From this a fresh vaccine was prepared. Following the drainage a fistulous tract developed through the abscess into the rectum. By January 14, inflammation had subsided and bowel movements had been reduced from a maximum of eighteen in twenty-four hours to six. Again he was dismissed. Improvement was steady. He returned for reexamination September 4, at which time the proctoscope revealed the mucosa still granular; the sinus tract had practically healed. January 3, 1927, tonsillectomy was done without incident. His weight at this time was 167 pounds and he was averaging three to four daily bowel movements and he felt well.

Case 5, nephritis and nephrosis.—A man, aged thirty-two years came to the clinic April 12, 1928, with a history of bloody dysentery of ten years' duration. His trouble had begun with bloody bowel movements and severe abdominal cramps after six months' service in the United States Navy. During the first three or four months of his trouble his weight had fallen from 140 to 90 pounds. He was not sure of the exact number of bowel movements but frequently they were as often as once an hour, day and night. Appendicostomy had been done—after he had been sick about six months and irrigations of ichthyol were given through the appendicostomy opening. In three or four months he had been free of symptoms. A year later his trouble had recurred in a way similar to the former onset. It had been mild then until the summer of 1921 when the bloody diarrhea had become worse. Cecostomy had been done but improvement had not followed and the cecostomy opening had been closed. A year later colostomy had been done but the opening had been closed fifteen months later. Progress had not been satisfactory; therefore colostomy had been done a second time. In January, 1927, a course of medication had been begun, but improvement had not resulted.

The patient's symptoms continued and on admission to the clinic April 12, 1928, he gave a history of progressive increasing bloody discharges for which he had had ten major surgical procedures. He presented himself with a malfunctioning cecostomy opening and much dehydration, continuous vomiting and symptoms of intestinal obstruction. After intravenous administration of glucose and withholding of food by mouth, his condition improved markedly. The obstruction relieved itself and his progress was such that examinations concerning the nature of the disease could be instituted. At this time albuminuria was graded 3, hyaline casts 2, granular casts 3, and pus 1. The blood urea was 114 mg. for each 100 c.c.; the blood chlorides, 543. Hemoglobin was 46 per cent, erythrocytes numbered 3,030,000 and leukocytes 6,700 in each cubic millimeter of blood. Of the leukocytes 49 per cent were polymorphonuclear neutrophiles. Systolic blood pressure was 140, the diastolic 80. In the ensuing fifteen days, progress was very satisfactory. The blood urea was reduced to 33 mg. for each 100 c.c., and the weight rose from 117 to 129 pounds as diet was increased. The combined phenolsulphonephthalein test of renal function gave a 15 per cent return of the

dye injected April 13, 18 and 25, respectively. Repeated examinations of stools revealed large amounts of pus and blood but no parasites or ova. Seven urinalyses in twelve days gave essentially the same results as those noted on admission except that in some of the specimens there was a slight reduction in the number of casts and erythrocytes. With the proctoscope, it was seen April 14 that the bowel was contracted to about a third of its normal diameter and that there was much scarring and that bleeding was induced with slight trauma. A diagnosis of chronic ulcerative colitis, grade 2, was made. The roentgenogram showed involvement of the entire colon, with very marked contraction and narrowing, and at many places the lumen was only a few millimeters in diameter. Vaccine was given subcutaneously for two months. The patient's condition improved markedly and there was marked lessening of the rectal discharges. Examination of the blood June 11 revealed hemoglobin of 67 per cent; erythrocytes numbered 4,320,000 and leukocytes 8,500 in each cubic millimeter of blood. Because of the recurrent attacks of obstruction at the site of the cecostomy and because it seemed hardly possible that the colon ever would assume a useful function, ileostomy was done, June 19, 1928. The postoperative course for the first seventeen days was uneventful. At this time the output of urine decreased and repeated examinations of the urine showed albuminuria graded 4, hyaline casts 4, granular casts 3, erythrocytes between 1 and 2 and pus between 1 and 2. Blood urea July 13, the day it was at its maximum, was 181 mg. for each 100 c.c. The chlorides were reduced to 417 and the carbon dioxide combining power to 46 volumes per cent. Glucose was administered and by July 28 the blood urea had dropped to 82 mg. Progress of the patient after that was continuous, and by August 22, the time of dismissal, the blood urea had been reduced to 43 mg. for each 100 c.c., and creatinine to 3 mg. The patient's general condition seemed good. He was on a limited intake of fluid. His bowels seemed to be in good condition; there was very little discharge and only an occasional trace of blood. He was gaining weight. A report in November stated that he had returned to work.

Case 6, endocarditis.—A man aged fifty years came to the clinic January 24, 1925, with a history of severe bloody diarrhea of four months' duration. It was found that in his early childhood he had had attacks of diarrhea that had come on about every six months. During this time he would have three to seven stools daily.

At the time of proctoscopic examination chronic ulcerative colitis was noted. By roentgenogram this was found to involve the entire colon. Roentgenograms of the stomach and chest were negative. Hemoglobin was 68 per cent, erythrocytes numbered 3,610,000 and leukocytes 8,100 in each cubic millimeter of blood. The blood urea on two examinations was, respectively, 20 and 14 mg. The Wassermann reaction on the blood was negative. The blood pressure was 86 systolic and the diastolic pressure was not satisfactorily obtainable. The course of the patient while in the hospital was progressively downward and he died, February 14, 1925.

Postmortem examination revealed: (1) chronic ulcerative colitis; (2) chronic mitral endocarditis with an acute exacerbation, and (3) infarcts in both kidneys.

Case 7, splenomegaly.—A boy aged fifteen years came to the clinic in June, 1928, with a history of bloody dysentery of four years' duration. He had passed about twelve stools daily; some days he would have as many as fifteen. Two years previous to his coming to the clinic, his home physician had found that he had had a large liver.

The patient was anemic, and appeared slightly yellow. His usual weight of 117 pounds was reduced to 102 pounds. Systolic blood pressre was 114 and diastolic 82. The pulse rate was 82 and the temperature 99.2° in the afternoon. In the upper left portion of the abdomen a large, movable, firm mass, thought to be the spleen, was palpable. The hemoglobin was 40 per cent; erythrocytes numbered 3,390,000, and leukocytes 7,200 in each cubic millimeter. Of the leukocytes 69.5 per cent were polymorphonu-

clear neutrophiles. Urinalysis gave essentially negative results. Parasites, ova or acid-fast bacilli were not found in the stools. The Wassermann reaction on the blood was negative. Acid-fast bacilli were not obtained from the ulcers in the rectum. The serum bilirubin, prothrombin time and fragility tests were negative. The tonsils were infected and one tooth had periapical infection. Roentgenograms of the colon following barium enema showed the deformity characteristic of chronic ulcerative colitis of the entire colon. The proctoscopic examination also revealed chronic ulcerative colitis, graded 2, with an annular stricture less than 1 cm. in width, 7 cm. from the anus. The advisability of splenectomy was discussed, but it was thought best to treat the severe colitis first and observe the effect on the spleen. The patient did not improve satisfactorily on the usual treatment and August 9 he experienced acute pain in the left lower portion of the abdomen with increased bleeding by rectum, and examination revealed a sausage-shaped mass in the left lower quadrant along the line of the colon. It was noticed at this time that the spleen had become reduced to at least half of its size on admission. A diagnosis of subacute perforation was made and operation was advised. August 12 ileostomy was performed. After a stormy course the patient died, August 17.

On postmortem examination, the following were found: generalized peritonitis, weight of spleen 537 gm., weight of liver increased to 1,185 gm. by hypertrophic juvenile cirrhosis, and a perisigmoidal inflammatory mass with extensive chronic ulcerative colitis.

Case 8, ocular inflammation.—A man aged fifty-two years came to the clinic in November, 1928, with a history of intermittent attacks of diarrhea associated with passage of blood, pus and mucus. This condition had endured since August, 1920. It had begun with four or five loose stools daily and the condition had grown progressively worse until, in October, 1920, he had been hospitalized and treated with irrigations of silver nitrate and a very limited diet. At this time a proctoscopic examination and roentgenogram of the colon resulted in a diagnosis of ulcerative colitis. Repeated examinations of stools failed to reveal amebae or bacilli of tuberculosis. The patient gradually improved and by the first of the following year seemed well and remained free from bowel trouble until August, 1922. The trouble increased so that December 18, 1922, cecostomy was done, followed by irrigations with silver nitrate through the cecostomy opening. The symptoms were relieved in about three months, and the cecostomy opening closed spontaneously. Following repeated recurrences of the trouble the worst attack had started in August, 1928, with three to five loose stools which had contained pus, blood and mucus. The condition had become rapidly worse, and in October the bowel movements had averaged in twenty-four hours twenty loose rectal discharges containing blood and pus. There had been marked tenesmus and daily fever. Examination in New Orleans had shown a granular, ulcerated, bleeding mucosa involving the sigmoid and rectum. Parasites or ova had not been found in the stools. A diagnosis of ulcerative colitis had been made and local irrigation had been begun. The symptoms had continued without improvement. During the month of local irrigations he had lost 20 pounds in weight and November 13 he had noticed a tender place near the rectum, the tenderness of which had increased hourly.

On admission to the clinic November 16, 1928, the patient was acutely ill and entered the hospital with a temperature of 103°, and a rapid pulse. To the right of the rectum was an acutely tender abscess, rupture of which seemed imminent. There were many rectal discharges containing pus and blood every twenty-four hours. Proctoscopic examination resulted in a diagnosis of severe, extensive ulcerative colitis, with an activity of about 2+, and an acute perirectal abscess just anterior to the anus. At this time his general condition seemed favorable for treatment. The blood pressure was 115 systolic and 80 diastolic and the pulse rate was 90. Leukocytes in each cubic millimeter numbered 15,200 of which 86 per cent were polymorphonuclear leukocytes. The

blood urea was 28 mg. in each 100 c.c. It seemed obvious that there were two conditions to treat, an acute perirectal abscess and severe chronic ulcerative colitis. Local application of heat to the rectum and deep injection of the concentrated serum into the muscles were begun. The abscess opened spontaneously on the third day of his stay in the hospital and following this there was much drainage of purulent material from the rectum and the abscess cavity. Examinations of the stools and drainage material for parasites and acid-fast bacilli were negative but culture of each yielded the usual diplostreptococcus found in patients with chronic ulcerative colitis.

Three weeks after admission acute redness and swelling of the left eye developed. In consultation with the ophthalmologist a diagnosis of marginal keratitis and acute iritis was made. Treatment of this was instituted at once. The patient recalled at this time that he had had a similar condition with the former upset of the bowels in 1922. Because of the acute condition of the bowels, it did not seem advisable to make a roentgenogram of the colon until December 1. When made, however, it showed subacute ulcerative colitis of the entire colon. The patient's progress was slow but progressive. Fifty-two days after admission he was dismissed; the abscess was practically healed and two to four formed stools without blood were being passed daily. He was advised to return for observation in about six months.

Case 9, fatal hemorrhage.—A man aged thirty-nine years came to the clinic, January 19, 1922, complaining of intermittent diarrhea which had persisted over a period of twenty-five years. He had been at The Mayo Clinic in 1902, at which time he had been given some medicine which had not relieved him. He was having between three and five fluid, light-colored, frothy and blood-streaked stools a day. Since 1900, he had been confined to bed for from two to six weeks with each of three severe attacks of diarrhea; during these attacks he became weak, emaciated, and could not work for months afterward. In the last few years he had become worse and he had had difficulty in controlling the bowels. There had been much tenesmus, backache, and pain in the rectum. Herpes labialis with sores inside the mouth often had accompanied the attacks. He did not remember having had fever, chills or sweats. There had been much accumulation of gas and occasional emesis.

The patient was fairly well nourished and weighed 138 pounds. The systolic blood pressure was 100, and the diastolic 60. The temperature was 98.4° at 9:30 a. m. There was slight tenderness of the lower portion of the abdomen and the sphincter ani was practically functionless. At this time total gastric acids were 70 and free hydrochloric acid was 50. The hemoglobin was 60 per cent; leukocytes numbered 8,300 and erythrocytes 3,710,000 in each cubic millimeter. The roentgenogram showed that chronic ulcerative colitis involved the entire colon. The roentgenogram of the chest was negative. Proctoscopic examination revealed chronic ulcerative colitis and rectal stricture; the latter was about 4 cm. above the anus and was 1 to 2 cm. wide.

Treatment consisted of irrigations with hot physiologic solution of sodium chloride, instillations of olive oil and bismuth, a rather generous diet, oxyquinolin sulphate (chinosol), instillations of witch hazel and benetol, and emetin hypodermically.

The patient was dismissed February 20, 1922, somewhat improved, and returned two years later, at which time he said the diarrhea had continued without much change, the bowel movements varying between six and twelve in twenty-four hours. He complained again about stabbing pains at the costal margin posteriorly. These had become much more severe since he had been in the clinic last and they continued for an hour or so at a time. The pains would come on suddenly, reached their maximum in thirty minutes, continued steadily and intensely and were so severe that he would roll on the floor with pain. His family and his physician said he was jaundiced after one of these attacks.

At examination hemoglobin was 25 per cent; erythrocytes numbered 2,300,000 and leukocytes 6,300 in each cubic millimeter. Polymorphonuclear neutrophiles were 64 per cent. Coagulation time was ten minutes

and bleeding time one minute. The patient belonged to blood group 4. Calcium coagulation time was nine minutes. The Wassermann reaction on the blood was negative. The tonsils were infected. The roentgenogram of the colon revealed chronic ulcerative colitis and stricture of the sigmoid. February 27 and March 4 and 11, respectively, he was given three blood transfusions and March 17 a permanent ileostomy of the modified Brown type was made. Postoperative progress was not satisfactory. There was a gradual rise in fever, increased weakness and a feeling of exhaustion. He died March 22, 1924, at which time the colon was filled with blood (2,000 c.c.) and there was also terminal peritonitis.

Case 10, *renal calculi.*—A woman aged nineteen came to the clinic in October, 1920, with a history of bloody dysentery of three years' duration. The first attack lasted five months with a maximum of twelve stools in twenty-four hours. She had a remission of about one month after which the trouble recurred. Her condition was worse during the winter. Increase in the number of stools and cramps often occurred during the night. She passed blood, mucus, pus and loose stools even when she was at her best, and during the three years the smallest number of stools had been three to four a day. During the winter previous to admission she had had much trouble with arthritis; the joints affected included ankles, elbows and knees, which had been swollen, stiff and very tender. At this time she had first had spells of pain in the right loin, so severe that her face would be drawn and she would talk incoherently. These attacks would last one to two hours.

On admission she was having about twelve stools in twenty-four hours. She was thin, emaciated, anemic and had lost 35 pounds in weight in the three years. The hemoglobin was 36 per cent; erythrocytes numbered 3,850,000 and leukocytes 17,600 in each cubic millimeter. Except for a trace of albumin, a few erythrocytes and 10 to 25 pus cells in each high powered field, urinalysis was negative. Parasites, ova or acid-fast bacilli were not found in the stools on repeated examination. Proctoscopic examination revealed chronic ulcerative colitis with the lumen of the bowel reduced to a fifth the usual dimension, and marked activity of the process. Because of the marked narrowing of the bowel and the history of continued trouble, ileostomy of the modified Brown type was done November 3, 1920. The postoperative course was uneventful and the patient got along well with the ileostomy opening. She returned to the clinic in November, 1925; she had gained 10 pounds in weight, in general felt well and hoped that she might have the ileostomy opening closed. She said, that a year after leaving the clinic she had had an acute flare-up of arthritis and that most of the joints had been involved. There had been frequent flare-ups of the colonic condition, with blood, mucus, and pus discharging from the rectum. There had not been any more attacks of the severe pain in the right side, but there had been spells of frequency and burning on urination without hematuria.

In four examinations of urine on as many days albuminuria was graded 3, erythrocytes 3, and pus 4. Two of these specimens were obtained by catheterization. Test of renal function gave a return of 40 per cent of the dye injected. Several urinalyses were negative for acid fast bacilli. Infected tonsils were removed September 7. Roentgenograms of the kidneys showed the presence of huge, bilateral renal stones. At this time it was noted also that the patient had papular cutaneous lesions of the extremities and hips. These had appeared in three attacks with exacerbations of the colitis. The lesions were papulonecrotic tuberculids.

In summary, then, the patient had extensive, chronic ulcerative colitis with rectal stricture, arthritis, bilateral renal stones and papulonecrotic tuberculids. Her general condition seemed fairly good, and the treatment consisted of a series of injections of neo-arsphenamine, vaccine subcutaneously, and symptomatic relief of the symptoms referable to the bladder. The last report from her, in 1928, showed that her condition had continued about the same.

Case 11, *mesenteric thrombosis.*—A girl aged fifteen years came to the clinic early in February, 1923, with a history of dysentery of one and a half years' duration.

The trouble had started after a camping trip and she had suffered from what seemed to be ordinary "summer complaint," but the condition had continued. There had been six daily stools with mucus, but without blood and pain. There had been a gradual increase in the trouble until she had had eight to nine stools a day containing mucus and blood. Reclining had not affected the frequency of the stools. Various medicines used had given slight, if any, temporary relief. Diet did not have any appreciable effect on the symptoms. She had lost about 6 pounds in weight and on admission weighed 99 pounds.

The blood count was essentially normal except that leukocytes numbered 10,000 in each cubic millimeter. A roentgenogram of the chest was negative and that of the colon showed the deformity of chronic ulcerative colitis. Repeated examinations of the stools were negative for parasites, ova and acid-fast bacilli. The proctoscopic examination revealed chronic ulcertative colitis with an activity of 3 on a basis of 4. A special examination of the heart was made. Medical management with local irrigations and tincture of iodine by mouth did not give apparent relief; in fact the patient seemed to be worse at the end of a month's treatment. Appendicostomy was done March 5, 1923, and about two-thirds of the appendix was removed. The patient's postoperative progress was only fair at first and later there was progressive failure. She died April 19, 1923.

The postmortem diagnosis was chronic ulcerative colitis of the entire colon, with anemia and acute enteritis of the terminal ileum, emaciation, graded 3, and extensive intra-abdominal venous thrombosis.

Discussion

Chronic ulcerative colitis is a serious infection of the colon. Its early diagnosis is imperative. This means careful examination of stools for parasites and unusual bacteria, observation of the stools for blood, mucus, and pus, careful consideration of the time of passage of stools and the conditions of tenesmus, urgency, and pain with evacuation of the bowels. Passage of blood, mucus and pus by rectum is unnatural. Careful inquiry into conditions which existed early in the period over which blood, mucus and pus were observed in the stool usually gives definite and important diagnostic data.

Proctoscopic examination should be employed in all cases of diarrhea, of discharge of blood, mucus, or pus by rectum, or of any rectal bleeding.

A roentgenogram of the colon after barium enema is the next most valuable diagnostic aid.

Finally, the importance of taking a careful history in all cases suggesting colonic disease stands out as the most important diagnostic aid.

With early diagnosis early treatment can be instituted and many of the serious complications can be avoided.

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Atypical Clinical Forms of Trichiniasis*†

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TRICHINIASIS in this country is far from being a rare disease, yet it seems not to have established itself in the mind of the average practitioner as one of those diseases to be thought of and watched for. For this attitude there are doubtless many reasons, but one of these seems to be the fact that there still exists the feeling, carried over from the early writings upon the subject, that trichiniasis occurs usually in the form of epidemics; whereas in point of fact most of the cases met with occur either as sporadic isolated examples or in groups of only two or three.

Another of the reasons for the common failure to recognize the disease lies in the fact that trichiniasis presents a clinical picture of much greater variability than is the case of most specific infectious diseases.

It is the purpose of this discussion to call attention to some of the many variations from the conventional and readily recognizable clinical picture. These variations have long been known and are referred to in most text book articles on the subject, notably in the admirable review of the subject by George Blumer,[1] but they seem sufficiently important to justify their further consideration.

During the past 15 years there have been treated in the medical wards of the New York Hospital 52 patients in whom the diagnosis of trichiniasis was made.* It is interesting to note that 47 of these cases occurred as isolated instances of the disease and that no history of others having been infected could be obtained. Of the remaining five patients three were members of one family and two were young women who lived together. Among such sporadic cases the graver types of the disease seem much rarer than is usually the case in the larger epidemics. No deaths occurred among the 52 patients referred to.

Before discussing the atypical clinical forms of trichiniasis it will be necessary to review briefly the usual clinical picture.

The resemblance of the average case to that of a mild or moderately severe case of typhoid fever has often been pointed out. There is usually a fairly abrupt onset, with fever, headache and malaise, and either with or without gastro-intestinal symptoms. The febrile period may last from a week or ten days to several weeks, the fever usually ranging fairly high and falling

*With the kind permission of my colleague Dr. W. R. Williams I have included with my own those cases that have occurred upon his service.

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by lysis. The prominence of muscular pain and soreness as a symptom varies greatly. Such pain and stiffness may be conspicuous and protracted, may be widely distributed or limited to special groups of muscles, or may be almost entirely wanting. Subcutaneous edema is a common and important early symptom that is usually fleeting and is often only recognizable about the eyelids and face. It is by no means always present however even in the early days. Cough, sweating and injection of the conjunctivae are among the common symptoms. The spleen ordinarily is not palpable. One of the most important diagnostic features of the disease is the early and marked increase in the eosinophile leukocytes, associated usually with some degree of leukocytosis.

With this brief description of the usual, conventional clinical picture we may now turn to a consideration of the unusual clinical types.

Atypical Clinical Forms

In general it may be said that no one of the above-named symptoms is essential or constantly present, and that any one or several of them may be lacking, or at least may be so inconspicuous as to pass unnoticed.

Cases Without Fever.—Although fever of some degree is perhaps the most constant of all the symptoms the almost complete absence of fever is seen in two types of cases, (1) those extremely mild or symptomless cases seen among the members of an infected family, which are recognizable only by the characteristic changes in the blood picture, and (2) cases with a very protracted course in which the chief symptom is localized pain or soreness. In some of these, by careful questioning, a history of an onset with mild fever and malaise may be obtained but in other instances the diagnosis may have to rest only on the history of an initial edema of the face, the presence of the characteristic high eosinophilia and, perhaps, the demonstration of the parasites in the excised muscle.

Occasionally after an initial gastrointestinal attack there may be an interval of several weeks with little or no fever before a period of continued fever ensues.

Cases With No, or With Only Very Late, Eosinophilia.—The constant presence of a high proportion of eosinophilic leukocytes in the blood has come to be looked upon as so essential to the diagnosis of trichiniasis that the absence of such an eosinophilia is apt to be regarded as sufficient ground for the rejection of this diagnosis. In general such an attitude is justified, but it must be emphasized that this rule of a high eosinophilia is by no means absolute. Bartlett[2] records an interesting case, fatal after seven weeks of illness, in which, although there was a leukocytosis of from 19,000 to 20,000, the eosinophiles did not rise above one per cent. The diagnosis was confirmed by autopsy and a histological study of the inflamed muscle showed round-celled infiltration composed of polymorphonuclear neutrophiles and small mononuclears, with only an occasional eosinophile cell. Similar fatal cases without eosinophilia are reported by Howard[3] and by Maase and Zondek.[4] Such an absence of eosinophilia throughout the

entire course of the disease seems however to be very rare. Of more frequent occurrence is the failure of the eosinophiles to appear until several weeks after the onset of the illness.

Gregg[5] cites the case of a boy of 11 years, severely ill and suspected of having typhoid fever, who showed no eosinophile cells until more than three weeks after the onset. Several days before the appearance of an eosinophilia a piece of excised muscle had shown the presence of many of the parasites. Cabot[6] refers to a case in which there was absence of eosinophilia during the first ten days of illness.

A woman on the service of my colleague, Dr. W. R. Williams, ran a febrile course, with edema of the face and legs, for six weeks before the advent of an eosinophilia. Several days before this occurred the excised muscle had revealed the presence of trichinellae.

Case I.—Among my own cases is that of an Italian boy of 11 years who, after an illness of three weeks, was referred to the hospital with the diagnosis of acute nephritis. He had had continuous slight fever, vomiting, lumbar pain and profuse sweating, as well as a marked subcutaneous edema which at the time of admission to the hospital was especially pronounced about the face and eyes. The urine however showed only a trace of albumin and a rare granular cast and various renal function tests yielded fairly normal results. In spite of the fact that the blood showed no eosinophiles whatever it seemed probable that the case was one of trichiniasis and frequent blood examinations were made. Five days after admission, among 7,200 white cells, there were three per cent of eosinophiles. This count remained unchanged until nine days later (i.e. five weeks after the onset) when the percentage of eosinophiles suddenly rose to 28. By that time most of the symptoms were subsiding. Ultimately the eosinophiles reached 36 per cent of a total leukocyte count of 16,000. A biopsy revealed many encysted larvae.

From the instances cited above it is clear therefor that even so characteristic and constant a symptom as eosinophilia may occasionally be lacking entirely or may appear only several weeks after the onset of the acute symptoms.

Cases Showing a Positive Widal Reaction.—The close resemblance of the clinical picture of many cases of trichiniasis to that of typhoid fever has already been referred to. This resemblance is usually confined to the general course of the fever and to the associated constitutional symptoms. Occasionally the similarity is made closer by the presence of a splenic tumor and of a scanty eruption over the trunk which bears some resemblance to the rose-spots of typhoid fever. In rare instances however the resemblance becomes even more confusing because of the presence of a positive Widal reaction.

Case II.—A man, aged 42 years, was admitted to the First Medical Division of the New York Hospital after six weeks of illness beginning abruptly with headache, nausea and dizziness. This onset was followed by a diarrhea lasting a week or ten days and by muscular pains and great weak-

ness. He had noticed no swelling of the face or eyes and thought he had had no fever. His temperature, on admission, was 102° and he continued to have a moderate fever for three weeks. The spleen was not palpable but over the abdomen were several small pinkish spots resembling rose-spots. The blood showed a leukocytosis and the eosinophile cells, which at first were only three per cent of the total, gradually increased to 43 per cent. Repeated Widal tests always gave a strongly positive Widal reaction and at one time complete agglutination was obtained in a dilution of 1 to 2,560. Agglutination tests with B. paratyphosus A and B, with B. coli and with B. dysenteriae were all negative. Many fruitless efforts were made to recover B. typhosus from cultures of the blood, stools and urine, and of bile obtained from the duodenum. Trichinella larvae were demonstrated in muscle obtained from the lower end of the biceps.

If this case were considered alone one might be inclined to feel that, in spite of the many unsuccessful efforts to prove the existence of typhoid fever, an infection with B. Typhosus must have been present along with the trichiniasis; but the case does not stand alone. Maase and Zondek[4] have reported three typical and fatal cases of trichiniasis in each of which the Widal reaction was positive in a dilution of 1 to 400, and in each of which the autopsy proved the existence of trichiniasis and the absence of typhoid fever. They note, however, that in spite of the strongly positive reaction to the Widal test, the response to Ficker's modification of that test (with dead bacilli) was negative. None of the patients had ever received prophylactic vaccination against typhoid.

In a second case of proved trichiniasis in the New York Hospital series (from the service of Dr. Williams) the first two Widal tests were negative, a third was definitely positive and a fourth, ten days later, was again negative.

There can be no doubt, therefore, that for some reason quite unknown, the serum of a trichiniasis patient may occasionally cause agglutination of typhoid bacilli even in high dilutions.

Cases Resembling Acute Nephritis.—In no symptom is there greater variation to be found than in that of the degree of subcutaneous edema present. Such edema may be lacking entirely or may amount to general anasarca. It usually appears first, and is most pronounced, about the eyes and face.

It is not surprising therefore that the rapid development of a generalized edema in an acutely ill patient should at first suggest acute nephritis. Throughout the literature of trichiniasis are frequent references to cases with pronounced and generalized subcutaneous edema. Cabot[6] speaks of a case in which there was not only general anasarca but dropsy of all the serous cavities as well. Case I furnishes a good example of this clinical type, in which the true diagnosis was further obscured by the fact that no eosinophilia appeared until five weeks after the onset of the illness.

Cases Simulating Meningitis.—J. Meyer reports three cases of trichiniasis, occurring in children of 6, 8 and 12 years respectively, which upon admission to the Cook County Hospital were sent to the Contagious Wards,

with the diagnosis of epidemic meningitis. In the most striking case there were delirium, marked irritability, photophobia, rigidity of the neck, a strongly positve Kernig's sign and absent knee jerks. In all of the cases, however, the spinal fluid was clear and had the characteristics of that of anterior poliomyelitis rather than of meningitis. The cells were increased to from 40-240 per c.m.m. In one case the trichinella larvae were recovered from the spinal fluid. In the case of Van Cott and Lintz,[8] in which recovery of the parasites from the spinal fluid is recorded for the first time, the patient had pronounced meningeal symptoms and a similar case is cited by McDonald and Waddell.[9] In the reports of several of the early writers emphasis is laid upon the frequency with which a positive Kernig sign and rigidity of the muscles of the neck are found in this disease.

Cases with Conspicuous Throat Symptoms.—Even in the early great epidemics in Germany it was noted that throat symptoms were sometimes very pronounced and that the laryngeal and throat muscles were apt to contain great numbers of trichina larvae.

Mackenty[10] has reported a series of three cases, infected at the same time, in which there were alarming symptoms of laryngeal obstruction. In the most striking case, a woman 60 years old, the patient was found propped up in bed, cyanotic and struggling for breath, with inspiratory stridor and a rapid, feeble pulse. Examination showed edema of the soft palate and of the lateral pharyngeal walls, extending over the epiglottis and obscuring the parts below. In addition there were pain and stiffness of the neck, jaws, face and tongue. The onset had occurred one week before, with fever, malaise, intense headache, diarrhea, muscular pains and severe, dry cough. The edema of the glottis subsided within three or four days and the diagnosis was established by a high eosinophila in all of the cases.

Cases Simulating Frontal Sinusitis.—Edema about the eyes, injection of the conjunctivae and soreness and pain on movement of the eyeballs are so common as to belong among the usual symptoms of the disease, but occasionally these eye symptoms may be so prominent as to dominate the clinical picture. E. L. Pratt[11] has recorded three cases in each of which the patient was referred to the rhinologist because of a suspected frontal sinusitis. There was edema of both eyes, but the chief complaint was severe pain over one frontal region. The absence of definite signs of sinusitis, together with edema of the eyes and the finding of a high eosinophilia led to the correct diagnosis. Thomas and Cooper[12] report the somewhat similar case of a man, ill for three weeks with fever, muscular pain and soreness, who developed great edema of the eyelids and complained of such severe frontal pain as to require morphine. Orbital abscess and empyema of the sphenoidal sinus were each suspected. The diagnosis of trichiniasis was established by the eosinophilia and the results of a biopsy.

Cases with Epigastric Pain as the Chief Symptom.—In the earlier writings on the subject of trichiniasis ref-

erences are occasionally found to cases in which epigastric pain has constituted the only symptom. The following cases from my own service are examples of this clinical type.

Case III.—An Italian man of 38 years was admitted to the hospital with the diagnosis of peptic ulcer. He had been well up to two weeks before, when he was seized with sudden sharp epigastric pain lasting about one hour. Thereafter these attacks of severe pain recurred several times daily, coming on usually after meals and lasting from 15 minutes to one hour. He complained of no other symptoms and was well enough to continue his work as a longshoreman. He had no fever, and the physical examination revealed only some puffiness about the eyelids and some tenderness in the region of the umbilicus. A gastro-intestinal X-ray examination was negative. The leukocytes however, were greatly increased (20,000-34,000) and the percentage of eosinophiles varied between 44 and 85. A bit of muscle excised from the lower end of the biceps contained trichinella larvae.

Case IV.—In a second case, also an Italian man, the patient two months before admission had had a sudden chill, followed by fever of two or three days duration. At the same time he developed muscular soreness all over the body which was so severe as to confine him to bed for two weeks. At the end of that time the general soreness disappeared but he began to have localized soreness, but not actual pain, in the upper abdomen, sometimes in the epigastrium and sometimes in the umbilical region. This discomfort, which had continued for six weeks, was not constant but would come on at irregular times during the day and bore no relation to meals. He had no fever and complained of no other symptoms. The abdomen was soft and free from tenderness. Gastro-intestinal X-ray examinations were negative and the only physical sign was some puffiness about the eyes. The leukocytes were not increased in number, but there was an eosinophilia which increased from 10 to 37 per cent. Although no parasites were found in the excised muscle, the slight edema of the face and the high proportion of eosinophiles seemed to justify the diagnosis of trichiniasis.

In cases such as these just described it has been customary, rightly or wrongly, to explain the epigastric pain by the assumption of a severe invasion of the diaphragm by the migrating parasites.

Summary

The usual clinical picture of trichiniasis is so characteristic and easily recognizable that the diagnosis in typical cases presents no difficulties; but there are many cases in which either the pathognomonic symptoms are so wanting, or the clinical picture resembles so closely that of other diseases, that mistakes in diagnosis are not easily avoided.

Some of the many possible variations from the conventional clinical type have been discussed and illustrated.

It has been shown (1) that some cases may run an afebrile course; (2) that in others the characteristic eosinophilia may be lacking, either throughout the whole course or for several

weeks after the onset of symptoms, and (3) that, rarely, the differentiation from typhoid fever may be rendered difficult by the presence of a strongly positive Widal reaction.

Among other atypical clinical forms considered are (4) cases resembling acute nephritis; (5) cases which simulate acute meningitis; (6) cases with conspicuous and alarming throat symptoms; (7) those simulating frontal sinusitis; and, finally (8) certain cases in which epigastric pain is the chief or only symptom.

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The Relation of Psychiatry to Medicine*

By Austen Fox Riggs, M.D., *Stockbridge, Mass.*

THE relation of psychiatry to medicine has, until quite recent years, been very unimportant, extremely tenuous, and quite unsatisfactory. Psychiatry has been considered, and with considerable justification, a very poor relation of medicine. This conception of its status is, however, largely a thing of the past, and as psychiatry itself has advanced, so also has its relation to general medicine. As a matter of fact I am not sure that further improvements in this relationship, to be immediately expected, will not have to come from the other side of the fence, so to speak, that is, from general medicine itself.

Nevertheless psychiatry even now is too generally thought of by most medical men as a narrow specialty, concerning itself only with so-called mental disease. On the contrary it covers a much wider field. It deals not only with mental disease but with all disorders of thinking and feeling, whatever their cause, whether in diseased brains or healthy brains; with all degrees of amentia and dementia; and with maladaptations to life, whether due to inadequate mental equipment or to inadequate use of a normal equipment.

To be more definite and specific, pyschiatry may be described as one aspect, or, if you prefer, a major expression of neurology, based in common with it upon the anatomy, physiology and pathology of the nervous system. Indeed these two, neurology and psychiatry, should always be hyphenated and thought of as one subject—neuro-psychiatry.

Far from being a narrow specialty, neuro-psychiatry is the broadest of all specialties, for just as the nervous system, which is its particular field, is the means by which all parts of the body are integrated and through which the body as a whole adapts itself to its environment, so neuro-psychiatry is the specialty which may often be used to integrate all other specialties.

The nervous system plays its important part in every disease, in every ill that flesh is heir to, and in the success or failure of every form of treatment. It seems obvious, therefore, that a specialty dealing with this great integrating system, with this all-important adaptor mechanism of the body, should enjoy the most intimate relation with general medicine. It has not in the dim past, but it surely will in the not too distant future, for medicine needs a full working partnership with neuro-psychiatry at least as badly as neuro-psychiatry needs such a relationship with medicine.

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There is no disease or disorder which does not in some degree affect the patient's emotional and mental life, nor is there any such condition which is not, in its turn, favorably or unfavorably affected by the patient's feelings and thoughts.

Though the pathology of a given pneumonia may present a microscopically identical picture with many hundreds of others, the mental and emotional effect it is having upon a given patient is unique to him, and the effect of these personal reactions of his upon the course of his disease may be of the utmost importance. You might perhaps neglect the orthopedic or dermatological aspect of the case but not the psychiatric, which may make all the difference between success and failure in the treatment of the case.

The patient with cancer of the breast may present the very same surgical problem as hundreds of thousands of others, but the significance to her of her disease, the significance to her of death, deformity, pain, and of every step of the proposed procedure will be in the aggregate unique, because it will be based upon her personality, her intelligence, her experience, her financial and social status; and the effect of her emotional reactions upon her physiological condition, upon her resistance to shock, indeed upon every item of the case up to and including its final outcome, may be profound. The gynecological aspects of the case may perhaps be safely neglected; there may be no reason for considering it from the aspect of any other specialty, save only psychiatry, but this side *cannot* be neglected with impunity.

It may not be appropriate or even wise to call in a psychiatrist to aid in the treatment of some diseases, but the physician or surgeon should at least have the psychiatric attitude. In many cases neuro-psychiatry should not be considered so much a specialty as an aspect, and a very practical and important aspect, of medicine itself, for the psychiatric point of view whether in diagnosis or in treatment, considers the individual and not just the disease, values the aid to be enlisted from favorable emotional reactions, values the intelligent cooperation of the patient, and fears the untoward effects of adverse suggestion, adverse emotion, and ignorance, both on the pathological condition and on the efficacy of the treatment itself.

As an example of the non-psychiatric attitude and of the great opportunities that may be lost by the consequent lack of intimate cooperation between medicine and psychiatry, I quote the following case:

The Medical Staff of a great General Hospital combined to treat a supposed duodenal ulcer in a middle-aged woman. She was suffering from an involutional depression with fixation of symptoms on her vegetative activities, as is often the case. The ulcer was never quite satisfactorily proved, but it was most sedulously and skilfully treated and cured. The opinion of her medical advisers was that the depression was due to the supposed ulcer and when that was cured the depression it had caused would disappear. They were surprised and genuinely chagrined that in spite of the good effects locally of the treatment, the patient took no interest in either

procedure or result. Discharged cured, she went home and died of her psychiatric disease—by taking poison. The necessity of the psychiatric point of view in this case needs no further comment.

Today the director of this great hospital has a psychiatrist on his staff, not as a consultant but as a regular attending physician who makes rounds with him, a cooperative arrangement which marks progress, of benefit not only to the internist and the psychiatrist but to every patient whom they serve.

As an example of how well such an arrangement works out in practice, the following case from another metropolitan hospital will serve. Here for the past two years a psychiatrist has been a member of the attending staff.

A young man was operated on for gastric ulcer. A gastro-enterostomy was done. The surgical recovery was excellent but the patient continued his post-operative vomiting. There was no apparent cause for this phenomenon. Every sort of medical treatment was tried without success. No sooner had the patient swallowed a few spoonfuls of his carefully prescribed diet than up they would come again. Toward the end of the week following the operation, the psychiatrist was asked to take a hand and see if he could do anything before an exploratory operation was resorted to. He found that the young man was highly neurotic, very suggestible and had somehow gathered the distinct belief that the purpose of the operation was to close the exit of the stomach and that therefore the only way left for food to get out of it was to come up. A simple explanation of the operative and anatomical facts, and of the effect this erroneous belief had had in continuing the vomiting was all that was required to ensure the patient's smooth and uneventful recovery.

Let these two cases suffice to illustrate not only the great advantage of a close relationship between psychiatry and medicine but that it may often become a factor of the utmost importance to the very life of the patient.

There is an enormously large class of cases in which neuro-psychiatry is not only important but necessary to medicine. I refer to the so-called functional disorders. It has been conservatively estimated that these constitute a very substantial majority of all cases seen in the medical out-patient departments of hospitals, as well as in the private consulting rooms of general practitioners. These disorders are of psychogenic origin with very few exceptions. They not only call for psychiatric understanding but are the very meeting ground of psychiatry and medicine.

An over-active colon may be due to a primary disturbance of its flora, but thousands of cases of so-called colitis are simply physiological expressions of an emotional state. In short, the "colitis" very often is merely an active, though sometimes obstructive, symptom of a far-reaching emotional disorder.

Likewise, the cause of some cases of hyper-thyroidism may be found in the patient's emotional life, rather than in a primary disturbance of one or more of his endocrine glands.

Many functional cardiac disturbances are notoriously typical neuroses.

In all of these cases the relation of psychiatry to medicine is of utmost importance, especially to the patient. Too often even in these modern days, the patient suffering from a neurosis goes from specialist to specialist with but temporary relief, only to fall finally into the more astute and less scrupulous hands of the charlatan because he, even though unscientifically and "as through a glass darkly," sees the psychiatric problem involved. When he too through greed and ignorance perhaps may lose his hold, and the neuro-psychiatrist finally gets his chance, the case by that time has reached a most unfavorable stage, for the patient has often lost faith in all doctors, in all science, and is mighty apt to take to pseudo-science, pseudo-religion or again to the best advertised charlatan.

The treatment of all neuroses and more obviously of all psycho-neuroses is of course primarily a psychiatric job, but the internist should at least be able to make a tentative diagnosis and help the patient to obtain suitable treatment promptly. Too often is this diagnosis made only after exhausting all and sundry possible medical and even surgical methods, and even then it is only reluctantly accepted and often with considerable undeserved contempt for the patient. Such a negative diagnosis, it might be noted in passing, is really no diagnosis at all. To say that a patient, because no other disease can be pinned on him, must therefore have a neurosis is not even logical. A neurosis is a real and recognizable disorder. It always has a cause, always functions in a more or less typical way, and an absolutely positive diagnosis should always be made. It cannot however be made without due consideration of these factors nor without adequate study of the patient's personality. Furthermore, medical treatment of a neurosis on a merely symptomatic basis does the patient absolute harm, for it places all the emphasis on the symptoms and tends to fix the neurosis and further entrench it against therapeutic attack. Obviously these cases should not be tinkered with by the internist even though he may have made a diagnosis, for they require all that the most skilful psychiatrist can give them. Here is where psychiatry can help medicine by assuming the major diagnostic and therapeutic burden, and here too is where medicine can cooperate most fully with psychiatry in evaluating the concomitant physical disorders and finding their treatment.

There is another function in relation to general medicine which neuro-psychiatry seems to be in a fair way of having to assume. I refer to the function of family adviser, which office used to be so well filled by the old-fashioned family physician and which now, by his lamented disappearance, is left practically vacant. The need is still there, indeed it is greater than ever in this day of extreme specialization. It is not satisfied by the most scientific and complete modern diagnostic survey by a group of specialists. Usually there is no one in the group or out of it who is sufficiently familiar with the patient's personal and family condition and problems to head the whole affair and steer the patient ac-

cording to his particular personal needs. By the very nature of his field the neuro-psychiatrist must know all that can be gleaned of the patient's family history, direct and collateral, he must have all the available facts of the patient's familial, social and financial conditions, as well as a full medical history. He is thus usually supplied with the necessary data. Unless some other more able and better fitted candidate for the position of family adviser appears, I think it most likely that the job will fall to the neuro-psychiatrist. Indeed I could quote numerous incidents from my own experience where this has already happened. In some cases the neuro-psychiatrist becomes the family physician because he has had to assume control in order to guide the patient, or the whole family, out of the labyrinth of unrelated and uncoordinated specialties. Sometimes he has been requested to assume the rôle, sometimes he has no doubt been accepted only "au faute de mieux." However that may be, the gap that the disappearance of the old time family doctor has left presents a problem which a closer relation between all specialties and particularly between psychiatry and medicine should go far toward solving.

But after all, that a closer relationship between psychiatrist and internist, between neuro-psychiatry and general medicine is greatly to be desired can hardly be doubted. It is so nearly self-evident that it needs little argument. But how can this be accomplished? How can the progress, already begun, toward a better relationship be accelerated?

The following possibilities of improvement suggest themselves:

First:—Let us begin at the beginning. Let us teach more neurology and psychiatry in the medical schools. Already in one of our leading schools these subjects are allotted slightly greater time in the curriculum than surgery. This is progress worth noting and an example worthy of emulation.

Second:—I would suggest following the good examples already set, by appointing neuro-psychiatrists on the attending staffs of hospitals wherever possible,—and using them. This advance would naturally be initiated by the internists in charge.

And Lastly:—I suggest that slow but sure method,—the education of the profession at large.

This may be done,—

First:—By including papers on neurology and psychiatry especially in relation to general medicine, at meetings such as this.

Second:—By including papers on general medical subjects, with especial reference to their relation to neuro-psychiatry, at meetings of neurologists and psychiatrists. The initiative should of course come from the latter.

Third:—By urging the members of the medical profession throughout the country to read the reports and journals of the mental hygiene organizations, so that they may familiarize themselves with at least the statistical facts in regard to the prevalence and increase of neuroses and mental diseases and disorders in this country at the present time. Few general medical men are aware of these facts. For

instance, how many know that more hospital beds are occupied today by those suffering from mental and nervous diseases than from all other diseases combined or that the number of unhospitalized psycho-neuroses is probably by far the greatest of all? A few such facts would make it quite clear to everyone that at least more than half of the enormous problem which modern life presents to medicine falls into the field of neuro-psychiatry, and that, furthermore, both neuro-psychiatry and medicine need all the help that either can get from the other to make headway against this problem, which neither can solve alone.

Psychiatry's Part in Preventive Medicine*

By Arthur H. Ruggles, *Providence, Rhode Island*

UP TO about fifteen years ago, psychiatry did very little that was actively preventive; its concern was largely with classification, the improvement in methods of treatment and the discussion of heredity vs. environment. With the advent of the Wasserman and the treatment of General Paresis with the arsenicals, and with the more general employment of lumbar puncture, Psychiatry learned that no case of syphilis could be considered permanently immune from neuro-syphilis unless repeated negative blood Wassermans were obtained following intensive intravenous therapy, and more especially unless it was determined over a period of at least two years following infection that the cerebrospinal fluid was not invaded. This was the beginning of a preventive effort regarding General Paresis and, while sufficient statistical study has not yet been completed, there seems to be evidence to show that in some mental hospitals the cases of General Paresis have in ten years been reduced from 10 to 12 per cent of all admissions to 8 to 10 per cent. I will not attempt to analyze this decreased percentage of G. P.'s, but believe it is in part due to the employment of preventive steps insisted upon by the syphilologist and psychiatrist.

At the time of the Great War the country was aroused from its self-complacent attitude by finding many thousands of our youth unfit for military duty by reason of mental defect, or of nervous or mental disease. In the years since the war we have seen nearly every state improve their facilities for the segregation of some of the feeble minded and for the community treatment of others. This is a step that in another generation should lessen the propagation of the mental defective, but in this particular direction we still have a long way to go and much to learn regarding prevention. The misnomer "Shell Shock" brought to the attention of layman and physician alike many cases of psychoneuroses that would otherwise have gone without understanding or treatment, and so we have recognized and cured many minor psychoses, as they have been called by some writers, and thus tended to reduce the number of nervous invalids in the community.

In the study of personality types we have come to recognize the schizoid and the syntonic, and thus we are better enabled in some cases to avoid the particular situations in life that would tend to push these individuals on into frank psychoses.

Yet you may say, "What evidence is there that psychiatry has done anything in preventive medicine when the total numbers admitted to mental hos-

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pitals are yearly increasing?" but so are the stress and strain of modern life, and so are the number of mentally sick persons admitted to hospitals who formerly roamed the streets or were secluded by the families at home. There are more general hospital beds filled with patients than there were ten years ago, but that does not mean that more people are annually sick, for we know typhoid fever, tuberculosis, diphtheria and many other diseases are much decreased today. It may take another quarter of a century before we can definitely demonstrate results in the prevention of mental disease, but that psychiatry is even today beginning to play an active part in preventive medicine I believe few can deny.

One of the preventive forces borrowed by the psychiatrists from the medical clinic, and developed to a very high degree, is the psychiatric social worker who investigates the social environment of our cases; who helps in the adjustment of the environmental situation when it is indicated as a measure of treatment, and who especially follows up cases leaving a mental hospital for a very long period of time. The assistance of the psychiatric social worker has been very great and serves as an indispensable part of the psychiatrist's armamentarium in his preventive measures. The psychiatric social worker has a recognized place in every well organized mental hospital, out-patient department and child guidance clinic.

Today every psychopathic hospital, and many of our state and private mental hospitals, have out-patient departments where large numbers of the psychoneuroses and psychoses are treated. Here the psychiatrist, the psychologist and the psychiatric social worker examine, investigate and carry on the treatment of psychoneurotics and of incipient psychoses, such as mild depressions, hypo-manic states, early schizophrenia, general paresis and other types of cases in which institutional treatment is not indicated; and thus many psychotic cases are readjusted or stabilized sufficiently so that they never need to go into a mental hospital. More and more the work of the mental hospital lies in the field of prevention and undoubtedly can best be met by the development of out-patient facilities. And in the mental hygiene movement as a whole, and perhaps more especially in the mental health program of individual states, no better policy could be established than that of for each dollar spent for building an equal amount be devoted to prevention.

Perhaps the best organized evidence of the attack on nervous and mental disease is in the schools of our country, and especially in the Child Guidance Clinics. At least fifteen large cities of this country have well organized Child Guidance Clinics where the pre-school and school child are thoroughly examined and treated by the psychiatrist, the psychologist and the psychiatric social worker. Most of the school systems of our cities, and many towns, have made provision for psychiatric examination of problem children. Here in Massachusetts there is a state law that requires the examination of all school children three years or more retarded; this is carried out by the staff physicians of the State

Hospitals. We know that 75,000 new cases are being admitted to mental hospitals each year; at the present admission rate that means 750,000 in the next ten years. From our knowledge of the average age of these patients on admission, we know that the majority of these prospective mentally sick are in our Grammar Schools and High Schools. The school psychiatrist is certainly in a strategic position to do preventive work, for we know definitely that certain mal-adjustments of personality not recognized or wrongly treated mean a larger psychosis, and that these cases can in many instances be so directed that nervous invalidism or the frank psychosis is avoided.

Perhaps one of the greatest contributions made by Psychiatry to Preventive Medicine is the insistence upon the understanding of the patient as a total human being with emotions as well as tonsils, with conflicts as well as a heart, and with thwarted purposes as well as a gastro-intestinal tract, so that we do not diagnose heart disease without understanding the total personality of the patient whose heart interests us, or do not take out the patient's tonsils to cure a psychic conflict. An illustrative case may make clear the point I wish to emphasize: a man of 32 came under my care because he had become afraid to leave his house unaccompanied or to be left alone in his home. For two years he had made his rounds of medical men with the result that the following diagnoses had been attached to him: Deviated nasal septum, eye-strain, gastroptosis, mucous colitis, varicocele and floating kidney. Is it any wonder he was afraid to be left alone? All of these conditions may have presented themselves to the examiners at various times, but a series of diets, belts, irrigations and operations could only have exaggerated his condition until the primary difficulty, which was a definite mental conflict, was understood and removed by treatment. I may have used an extreme case for illustration, but there are far too many nervous invalids being created today because the medical man fails to investigate mind as well as body, and then to evaluate the disorders that may be present in both fields. You may say, "But the psychiatrist thinks all disease is located in the mind"; not at all; the well staffed psychiatric clinic finds that a large percentage of mental defect has its basis in birth injuries, deafness, visual disorders and endocrine dysfunction. The psychiatrist knows that certain neurasthenic and hysterical symptoms may be the earliest manifestations of a brain tumor. Focal infections are not neglected; in fact, perhaps some of us have over-emphasized their importance. In a high percentage of all our cases we find causative factors in the blood picture, in the gastro-intestinal tract, in the gall bladder and in impaired kidney function. I shall never forget a delirious patient sent from the medical wards of a general hospital to a psychiatric hospital for care. A few days later the mental hospital made a diagnosis of central pneumonia, whereupon the referring physician at once said, "Of course, you will send the patient back to us for treatment of his pneumonia!" When it was explained that the physi-

cal disease would receive adequate treatment, and the mental symptoms better treatment than the general hospital could provide, the medical man expressed surprise, but the patient soon recovered in our mental hospital; and I honestly believe that many delirious patients die in the general hospital who would recover in the mental hospital, because of better understanding of the treatment of delirious states on the part of psychiatric nurse and doctor. Recently, in one of our New England mental hospitals, a case of undulant fever was diagnosed by a staff physician, this being the first case recognized in the whole state, so that the mental hospital cannot be accused of being medically unobservant or unprepared.

The psychiatrist today has a recognized place in the medical departments of schools, colleges and industry, in which fields the work is largely preventive.

It seems to me that psychiatry still has a very great contribution to make to preventive medicine in the field of a better understanding of the causation of some of the recognized mental diseases which, at the present time, fill a large proportion of our mental hospital beds. Since the days of Kraepelin's classification, which began more than a quarter of a century ago and which has been modified and improved, but not essentially changed, there have been, with the exception of the treatment of general paresis, the more careful correlation between physical and mental findings and the analytical approach to some of our cases, almost no real contributions to the understanding of the etiology of the psychoses, and it is high time that every psychiatric hospital with its wealth of controlled material should establish laboratories for an intensive attack on such important mental diseases as schizophrenia and the manic-depressive psychoses. Until this is done we will, I am afraid, have to concentrate our attack on mental diseases largely upon our attempts to adjust personality at earlier age levels, and to individualize and intensify our treatment of cases. A great number of research workers concentrating with all modern methods upon the study of a large group of psychoses whose etiology is at the present time unknown may, in the next quarter of a century, bring to medicine a better understanding of the essential factors underlying thousands of mental diseases, which would enable medicine to intelligently reach a large percentage of cases today occupying hospital beds.

Let me close with an illustrative case from my college mental hygiene experience. A freshman in college became depressed, unable to sleep and unable to study. He was sent to the Medical Hospital Department where it was found that he had no physical disease. His father had for years suffered from a manic-depressive psychosis, and the boy had always feared he might become a victim of the same disorder, so quite naturally when he became fatigued with hard study and working additional hours to earn money, he could not concentrate, his grades fell and he became depressed. When he saw the psychiatrist he was convinced that his father's future was before him. A readjustment of his working hours, better diet and general

physical hygiene, together with explanation and encouragement soon dispelled the depression, the boy got well and finished his year with high marks. In his second year emotional over stimulation of fraternity activity and competition for a position on a college publication brought on an attack of acute excitement that was recognized as a manic attack. Immediate rest in bed with mild sedatives promptly cleared this up, but it was felt that two mental upsets in two years made the situation serious. He was advised to go into the country for six months, which he did, and then advised to transfer from a large city college to a small college in a country town; here, competition of all sorts was less, reducing mental stress and strain, and he was graduated two years ago. He is now holding a good position (again without too much stress and strain), has had no recurrence of his trouble, and I will venture to predict will not, if he obeys the rules of mental health that apply to his make-up.

Without mental hygiene I am sure our mental hospitals would have added another to their list of cases; and, so, I believe that psychiatry is already contributing something to preventive medicine, and will have much more to contribute, if medical education trains all physicians to understand and treat the whole human being and not simply a diseased section of a case, and if psychiatry itself develops a group of physicians intensively laboring to better understand the causes of the mind diseased.

Relation of Streptococci to Influenza*

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Ann Arbor, Michigan

MUCH difference of opinion exists as to the causative organism or organisms of epidemic influenza. The general belief is that it is caused by the influenza bacillus, although many authorities are of the opinion that while this organism may be related to the infection, it is not the primary cause. With the development of our knowledge of the wide variety of clinical entities produced by the streptococci, different authorities have recently suggested that these organisms may be responsible for this disease. An opportunity was offered us during the recent influenza epidemic at Ann Arbor (Nov. 1928 to Feb. 1929), to carry out a bacteriological investigation of a group of influenza cases. The results of this investigation as well as more recent views of the causative nature of influenza will be discussed in this article.

If we look back to the influenza pandemic of 1890-1891, we find the description of the disease prevailing at that time described by Lichtenstern[1] as follows: "The typical influenza consists in a sudden fever, which is initiated by a chill or chilly sensation—lasting from one to several days, is associated with severe headaches (especially in the frontal region), vertigo, pain in the back and legs, disproportionately severe prostration and loss of appetite. After 10-12 hours, perspiration ensues and in 24-48 hours, the fever has usually subsided in many of the patients, leaving them with great weakness and with pains in muscles and joints which disappear in a few days. Symptoms of catarrhal inflammation of the respiratory tract often supervene upon the above manifestations."

Again, Zinsser[2] describes the cases of the 1918 pandemic in the following manner: "The early cases were clinically so uniform that a diagnosis could be made from the history alone. The onset was almost uniformly abrupt. Typical cases would become ill suddenly during the night or at a given hour in the day. A patient who had been perfectly well on going to bed, would suddenly awake with a severe headache, chilliness, malaise and fever. Others would arise feeling perfectly well in the morning and at some time during the day would become aware of headache and pains in the somatic muscles. Occasionally there was nausea. A few of the patients could state the exact hour at which they were taken ill. There were, of

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course, some cases in which the onset was more gradual."

Those who had occasion to see the influenza cases at the University Hospital will immediately recognize the above description as fitting these patients. The cases were invariably characterized by a sudden onset, fever, headaches, generalized aching and marked prostration, occasionally also nausea and anorexia. The course in the uncomplicated cases was usually a short one, the patients having a high temperature, 101° to 104° at the onset, which rapidly came down to normal within one to three days. The patients felt much improved on the third or fourth day and were anxious to return to work, although the majority of them experienced definite fatiguability upon exertion, for a considerable period of time.

The physical examination of a typical case presented striking and characteristic features. The patient appeared prostrated. The face was usually suffused and the eyes were watery, glistening and occasionally reddened due to the injection and inflammation of the conjunctivae. The throat examination revealed the fauces to be markedly reddened, glistening and usually dry. There was a sharp line of demarcation of the redness at the junction of the soft and hard palate around to the base of the anterior pillars. The tongue was characteristic in a great majority of cases—being usually furred, with the edges and tip clean, reddened and showing red swollen papillae.

In several cases, there was an erythematous rash of an intense hyperemic character on the chest and neck suggesting very strongly a scarlatiniform eruption. This rash was so characteristic in about six or eight cases that they were sent to the contagious hospital with the provisional diagnosis of scarlet fever. At least two patients who had very severe infections, with a pneumonia complication in one and an acute pansinusitis in the other, showed desquamation of the hands and feet during convalescence. Indeed it was this clinical picture which suggested a bacteriological study of these cases. It was believed that the Streptococci scarlatinae or closely related streptococci were possibly playing an important etiological rôle in these so-called influenza cases.

Bacteriological Study

The general plan of this study was to determine the predominant type or types of organisms found in the throats of influenza patients as compared with those found in non-influenza patients and in healthy individuals. When the colonies of any given organisms grown on blood agar plates were found to the extent of 50 per cent or more of the total growth, the organism was considered as predominant. It was believed that the presence of isolated colonies here and there of any given organism could not be interpreted as being of special significance since cultures of so-called normal throats frequently show such isolated colonies. Blood cultures were made on all influenza cases. Of these, only one showed positive findings, in the nature of streptococcus hemolyticus.* In a few of the influenza

*This was a post operative case which developed influenza complicated by bronchopneumonia and later septicemia.

cases showing complications, cultures were also obtained from the infected foci. A total of 142 cases was studied. These included 43 influenza patients, 11 influenza post-mortem examinations, 63 non-influenza patients and 25 student nurses who gave the history of not having had any respiratory infection or other illness during the past year.

The bacteriological findings are illustrated in Table 1. Of the 54 influenza cases, 44 showed a predominance of hemolytic streptococci and 7 of strep-

TABLE 1

INCIDENCE OF THE PREDOMINATING ORGANISMS IN INFLUENZA CASES AND CONTROLS

No. of cases	Types of Cases	Hemol. Strep.	Strep. Viridans.	Pneumo cocci.	Micro. Catarr.	Variety of Organisms
43	Influenza patients	33	7	1	2	0
11	Influenza post-mortem exam.	11 (100%)	0	0	0	0
63	Non-influenza patients	6	12	0	3	42
25	Healthy individuals	0	0	0	0	25
	% Streptococcus { influenza cases					94%
	% Streptococcus { control cases					20%

tococcus viridans. A total of 51 cases or 94% thus showed predominance of streptococci. The remaining showed a predominance of pneumococcus in one and Micrococcus catarrhalis in two. It is interesting to note that one case showed a pure culture of hemolytic streptococcus one day; in a second culture streptococcus viridans predominated, and a third culture again showed pure culture of hemolytic streptococcus.

Of the 88 control cases, 6 showed predominating hemolytic streptococcus and 12 showed a predominance of Streptococcus viridans. Considering the streptococci as a whole, the total incidence in these cases was 20 per cent. These control cases included 63 non-influenza patients suffering from a variety of diseases in the medical and surgical wards of the University Hospital, and 25 healthy individuals. All of the latter gave a negative history for previous influenza infection, and no upper respiratory infection within the last year. None of the throat cultures in these cases showed streptococci in predominance but showed a variety of organisms typical of normal throats.

It may be of interest to mention case P. A. He was a cardiac patient on the medical ward who had entered the hospital about two weeks previous to the day when control cultures of the non-influenza cases were taken. The throat culture showed 100% hemolytic streptococcus. Twenty-four hours after the cultures were taken, the patient showed typical symptoms and signs of influenza. Two days later he showed signs of bronchopneumonia and on the fifth day after the onset of the influenza symptoms, the patient died. No post-mortem examination was made.

Although the total number of influenza cases studied was relatively small, the high incidence of the streptococcus isolated would suggest that these organisms are etiologically related to this

infection. Whether they are the primary or the secondary agents, it is not possible to say. It is of interest in this connection to recall that Donaldson,[3] who has made an an extensive bacteriological study of the influenza pandemic of 1889 to 1892, concludes:

"1. That no type of organism was found common to all influenza cases.
2. Not only did one or the other of the organisms predominate in certain localities, but they were often found in pure cultures, causing the observers to hail it as 'the' cause of influenza.
3. Moreover, the bacterial balance in one locality was not always the same—at one period of the pandemic, the prevailing organism might be a streptococcus, at another, the pneumococcus.
4. Many of the organisms possessed pleomorphous characters."

With the announcement by Pfeiffer of his discovery of the influenza bacillus in 1892, bacteriologists throughout the world directed their attention to the study of this organism in connection with influenza. The result was that during the influenza epidemic of 1918, practically all effort was concentrated on the Pfeiffer organisms. In spite of this effort, the percentage of influenza cases showing Pfeiffer bacilli was relatively small. Donaldson[3] made a study of the bacteriological reports published in England, Germany, France, America and other countries of the 1918 influenza pandemic. According to this investigation, of 19,145 examinations made on influenza patients, only 34.4% showed the Pfeiffer bacillus. Of 3,056 postmortem examinations, about 40% showed this organism. A summary of Donaldson's figures relating to this pandemic is presented in Table 2.

It is seen from this table that the Pfeiffer bacillus was found in 30.3% of the healthy individuals and that the percentage of positive findings during the epidemic was higher in those suffering from non-influenza disease than those suffering from influenza. Based on these figures, Donaldson concludes: "Whatever was the cause of influenza, it was certainly not Pfeiffer's bacillus. If the infection was due to a common virus, the Pfeiffer bacillus was not even the most important secondary invader."

It was unfortunate that the pneumococcus and streptococcus groups were not studied with the same thoroughness in the 1918 pandemic, as was the Pfeiffer bacillus. This was due to the erroneous view that the latter was the

TABLE 2
INCIDENCE OF PFEIFFER'S BACILLUS IN INFLUENZA AND CONTROL CASES DURING PANDEMIC, 1918-1919, AND INTER PANDEMIC PERIOD

	Interpandemic Period	Pandemic Period
Influenza	29.2%	35%
Non-influenza diseases	40%	49%
Healthy individuals	18.6%	30.3%

primary cause and that all other bacteria were secondary invaders. Accurate figures were therefore not available, since many observers had either ignored the other organisms or had casually stated that they had not been noted. In Donaldson's[3] opinion, "the pleomorphous streptococci strains were more important pathological agents, as proven by serological tests. Many were highly pathogenic for animals, were more consistently virulent and resulted in illness more like influenza than that caused by Pfeiffer's bacillus. Hence, the pleomorphous streptococci behaved in a more virulent way and were found in a greater percentage of the influenza cases and should therefore rank more importantly even as secondary invaders, than Pfeiffer's bacillus. Insofar as the pleomorphous streptococcus was present in a far higher percentage of cases than Pfeiffer's bacillus, it has an even better claim at being *the* cause of influenza. Of course, in absence of sufficient data to prove Koch's first postulate that it must be found in all cases, this claim cannot be maintained." It is of interest to note that Pfeiffer's original studies were based on a total of only 31 cases.

Zinsser,[2] in a review of the Etiology of Influenza, states that the pneumococci and streptococci are probably not etiologically related to influenza. His reason is that since these organisms habitually inhabit the upper respiratory tract, they would be frequently isolated from influenza patients. He also concludes against the Pfeiffer bacillus theory, his evidence being:

1. Frequent failure of competent bacteriologists to find it.
2. The presence of the bacilli in the throats of normal individuals.
3. Their presence in pathological conditions not influenzal.
4. Frequent presence as complicating invaders as in Whooping Cough, Measles, etc.
5. The multiplicity of strains.
6. The infrequency of blood culture findings.
7. The unsuccessful attempts to produce the disease in human beings with pure cultures.

Modern bacteriology gives us a possible clue as to the relation of the streptococci to influenza. It has become recognized in recent years that bacteria are capable of passing through a life cycle and that at certain stages in this cycle, not only their morphology, but their physiological, cultural, serological and antigenic characters may undergo change. May it not be possible that the streptococci when in a special cyclogenic stage are capable of producing the syndrome of influenza?

Microbic dissociation has recently been summarized comprehensively by Hadley.[4, 5] Dissociation of bacteria most frequently occurs as a result of changes in their environment. Several cyclogenic forms have been isolated from single strains of organisms including the "R" or non-virulent form; the "S" or virulent form and, as is being attempted now, the "G" or filtrable form. In former days, pleomorphism meant to the orthodox bacteriologist that he was dealing not with one organism but with a mixture of organisms—possibly due to faulty technique. The modern bacteriologist, however, looks upon pleomorphism as

natural variations in the life cycle of the organism.

This conception of cyclogenic variation in organisms according to Hadley is destined to change our point of view of the etiology and epidemiology of infectious diseases. Etiologically, the virulence of a given strain of organisms depends on the predominance of the "S" or "R" forms. The same is true when considering the agglutinating properties of an organism. If, as occasionally occurs, a given typhoid strain is not agglutinated by anti-typhoid serum, it is no longer interpreted as an anomalous reaction but as a reaction with a cyclogenic form of the typhoid organism having different antigenic properties.

It is possible that the onset of an epidemic is caused by a change in an organism or in organisms from their non-virulent or inactive form to a virulent virostage, and that the remission of an epidemic is the passing into a non-virulent form. In the treatment of disease, future efforts will probably be directed toward the control of the cyclostage by studying how, in what sequence, and under what conditions of environment, cyclogenic variations have been and can be produced.

Applying the above bacteriological conception to influenza, the fact that 94% of the cases showed predominating streptococci would suggest the possibility that some dissociated form of these organisms—conceivably, a filtrable virus form—is the disease producing agent. Conditions of which we are as yet ignorant may be responsible for producing this dissociated form which initiates this disease. The only observations deserving serious consideration that influenza is caused by a filtrable virus are those of Olitsky and Gates.[6, 7, 8, 9] They have isolated from the nasopharyngeal secretions a minute filtrable bacillary organism which they call "Bacterium pneumosintes." Their data warrants further investigations of this organism.

In view of the clinical similarity of this disease to other entities caused by the streptococcus and because of the high incidence of the streptococcus in the cases examined by us, we feel that further study of the organism, perhaps from the point of view suggested by Hadley, is indicated.

Summary

A bacteriological study was made of 142 individuals during the recent influenza epidemic at Ann Arbor (Nov. 1928 to Feb. 1929). Of 54 influenza cases, 94% showed a predominance of streptococci, these consisting largely of the hemolytic form. Of the 88 control patients, 20% showed a predominance of streptococci. Studies on influenza have been heretofore directed largely to the Pfeiffer bacillus; paying comparatively little attention to the streptococcus group. The clinical picture of influenza and the high incidence of streptococci found in this study warrant further investigation of this organism in relation to this disease. When considering the dissociation which organisms undergo under different conditions, it is conceivable that the causative organism of influenza might be the streptococcus in some dissociated state, possibly a filtrable state.

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Lead Poisoning From Snuff*†

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NOTWITHSTANDING education, publicity, and restrictive measures lead poisoning has become the chief industrial hazard. Since compounds of lead frequently contaminate drinking water, beverages, cosmetics and a variety of other substances used by mankind, it has become equally as important a factor in causing distress and sickness among the non-industrial population. New sources of lead poisoning are constantly being uncovered so that it behooves the Medical Profession to be forever on the watch for this important disease and its manifestations. Within the past year another source of lead poisoning, while by no means new, should be newly emphasized in this country.

Model[1] in 1784 first drew attention to the possibility of lead poisoning from snuff-tobacco. In 1843 Otto[2] of Copenhagen reported two cases, one of which was fatal. The victim was a botanist and scholar, who suffered from obstinate constipation, abdominal cramps, headaches and who finally became comatose and died. Not until after his death was lead poisoning suspected and then an analysis of the brand of snuff he was in the habit of using, showed considerable lead. For some years following this a number of articles appeared in the foreign literature dealing with this source of lead poisoning, for in 1886 Billings[3] collected a total of 23 references, including 5 cases reported by Mayer[4] and 19 cases by Sonnenkalb.[5] About this time Garrod[6] in a clinical lecture on "Lead Poisoning" emphasized the possibility of lead poisoning occurring in warm climates when moist snuff is packed in lead covered boxes. He reported a case of an Englishman who had just returned to London from India on account of an illness, the cause of which was traced to lead found in snuff. In 1904 McCaw[7] added six more references, which included an interesting case of aphonia caused by lead poisoning from snuff reported by Ormsby[8] of New York. In 1912 Stadler[9] of Switzerland reported that a certain metal-foil wrapper contained 89.0% of lead and the moist snuff contained 1.75-1.90% of lead. Habitual use of this brand of snuff by a woman caused fatal intoxication. In 1918 four cases were reported in America, three cases by Uttal[10] of New York City and one case by Bauer and Ropes[11] of Boston. All in all about forty cases have been reported.

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There are three possible causes for lead in snuff-tobacco: (1) adulteration in manufacture, (2) lead wrappers, and (3) lead compounds used as insecticides.

The manufacture of snuff[12] consists in moistening tobacco leaves and stalks with salt water, and leaving them to ferment in an open chamber for some months. Then the tobacco is ground to a powder, moistened again and put into a closed wooden chamber to undergo a second fermentation process. This destroys about two-thirds of the nicotine, and the malic and citric acids in the tobacco, while the acid and bases evolved leaves free ammonia in the snuff. Various flavors are added to give scent. Quicklime is often used to give a biting, desiccating effect. Formerly lead oxide and chromate were added to give a lighter color and greater bulk, and thereby increase the sale value. Snuff is packed and marketed either in a dry or moist state, depending upon the amount of moisture added during the fermentation. In 1849 Hassel[13] examined 43 kinds of snuff; nine brands contained lead chromate in amounts varying from 1-4.5%; three specimens contained lead oxide. Since tobacco products do not come within the Federal Food and Drug Acts there is no adequate legislation to prevent adulteration at the present time.

Another source of lead in snuff and the one most referred to in the literature is due to the usage of lead-foil for wrapping and lead-tin boxes for packing. Stadler[9] (already referred to) reported 89% of lead in a metal-foil wrapper used for snuff even though the Swiss law prohibits a content greater than 1%. Wicke[14] found that the outer crust of snuff packed in lead-foil contained up to 2.7% lead even if the foil was lined with tin on one side. When the snuff is damp or contains acetic acid, absorption of the lead from the wrapper is apparently increased.

The third possible source of lead in snuff is due to the fact that lead-arsenate is used rather extensively as an insecticide in the growing of the chief types of tobacco used in the manufacture of snuff.[15] 1927 Remington[16] examined a large number of brands of American smoking and chewing tobacco and found arsenic to be invariable present in quantities many times greater than the amounts cited as being permitted in foods. It is possible that the source of the arsenic was due to the arsenate used in the plant spray and that lead may also find its way into tobacco for the same reason.

During the past year and a half I have seen four cases of lead poisoning from snuff. All were middle aged white women admitted to the charity ward of John Sealy Hospital. Analyses of the snuff, feces and urine of these patients showed lead. All chemical analyses were made by Professor B. M. Hendrix of the Department of Biological Chemistry. The patients all used the same brand of snuff which we believe was adulterated with lead chromate. The samples examined were marketed in glass jars.

The first case will be considered last. Case No. 2 has been free from symptoms now for about a year since she stopped taking snuff. Case No. 3, shortly after entering the

hospital died from an inoperable carcinoma of the cervix, hydronephrosis and uremia. She gave a history of taking snuff for 20 years. Twelve years previous to entering the hospital she had been advised to take radium treatment for her pelvic condition. What the diagnosis was at that time could not be determined. Post mortem examination confirmed the clinical diagnosis and a short while after the organs had been preserved in formalin it occurred to us to test certain of the soft tissues for comparative lead content. Analysis of the liver tissue showed 3.31 mgs. of lead per 100 gms. of tissue; heart muscle showed 4.42 mgs. of lead per 100 gms. of tissue, the carcinoma contained 7.34 mgs. of lead per 100 gms. of tissue. Not enough of the cancer was available for a duplicate determination, but we feel that the proportion of lead found in these tissues is reasonably correct. This suggests a greater affinity for lead on the part of carcinomatous tissue as compared to other soft tissues, but requires further investigation. Case No. 4 is in the hospital at present. She came in complaining of weakness, abdominal cramps and pains in her limbs. The snuff this patient was taking showed on repeated analysis 0.35% of lead chromate, or 0,224% lead.

Report of Case No. 1

November 4, 1927, Mrs. L. K. an Irish-American housewife, aged 44, came to the John Sealy Hospital complaining of weakness and vomiting.

Following an attack of "influenza" six months previous there had been increasing soreness and progressive weakness in her lower limbs. For two months there had been attacks of severe epigastric pains which were referred to the back. With the pain was nausea and vomiting irrespective of meals, until finally she was unable to keep anything on her stomach. Besides this there had been dizziness, increased thirst, constipation, oliguria, and edema of the feet. For some time her sense of taste had been impaired. At the beginning of her illness her weight was 250 pounds; at time of admission it was 180 pounds.

She had measles, mumps and typhoid fever when a child and at one time she swallowed lye, which resulted in an esophageal stricture, for which numerous dilatations were performed. At the age of 18 an "abscessed ovary" was removed. All her life she had drunk a fair amount of beer and for the past 2 years considerable whiskey. She had never been pregnant.

Physical examination showed a middle-aged white woman, apprehensive with a pained expression and pasty appearance. Teeth were dirty and the gums showed advanced pyorrhea. Tongue was coated, and the sense of taste for sweet and sour was impaired over the anterior two-thirds.

Cardio-respiratory system was normal except for hardening of the arteries and a soft blowing systolic murmur localized at mitral area. Systolic blood pressure was 120, diastolic 86. There was generalized muscular weakness. The lower limbs were flabby and extremely tender to touch over calves and thighs. Knee jerks absent. All the other reflexes were normal. Pelvic examination showed atrophy of vagina and uterus.

The urine was acid and showed a low specific gravity and an occasional hyaline cast. No albumin or sugar present. A satisfactory gastric specimen could not be secured. The vomitus showed bile stained mucous and little else. Red cell count was 4,350,000; Hgb. 75%. White cell count 7,900. P 71; L 27; Tr. 2. Wassermann negative. Basal metabolism normal. X-ray of esophagus and stomach showed no esophageal stricture, but there was delayed gastric drainage, and a dilated duodenal bulb with a tortuous and angulated second part, suggesting adhesions. Intravenous injection of tetra-iodophenol-thalein salts fol-

lowed by films revealed no gall bladder shadow.

On November 2nd, a cholecystectomy and appendectomy was done. The gall bladder was freed from adhesions reaching to the duodenum. Subsequently a pathological diagnosis of chronic atrophic cholecystitis was rendered.

Following the operation there was slight improvement and when the wound was healed she was allowed to go home.

On December 14th the patient was readmitted in a very weak and dehydrated condition. She had been unable to keep solids or liquids on her stomach since leaving the hospital. She now complained of sharp shooting pains in her hands and legs, with numbness and sensation of pins and needles in the fingers and toes. She appeared very much dehydrated; the skin was dry; eyes were sunken and the tongue was bright red in color. There was a marked atrophy of the interrossei muscles of the hands with incoordination of movement. The lower limbs were held in a flexed position and complete extension was impossible because of pain and spasticity. There was extreme muscular tenderness over the lower extremities. The slightest pressure on the toes caused excruciating pain. There were no signs of local inflammation.

Further laboratory work showed the phenolsulphonephthalein elimination by the kidneys to be 55% in 2 hours. A Mosenthal test showed the maximum specific gravity of the urine to be 1.006, with a variation of 5 points; the 24 hour amount was 2,760 cc.; the day to night ratio was 1:1. The red cell count was 3,720,000 and the hemoglobin was 60%. The white and differential count was normal. Basophilic stippling was present on an average of one cell to every two oil-immersion fields. The T. N. P. N. of the blood was 38 mg.; Uric acid 8.4 mgs.; creatinin 1.5 mgs.; chlorides 530 mgs.; Serum calcium 9 mgs.; per 100 cc. of blood. Spinal puncture showed a normal fluid pressure. There were 7 lymphocytes to the cu. mm. Globulin was markedly increased and the Wassermann was negative. Stool examinations were negative. X-ray examinations of the stomach, knees, spine, and pelvis were negative. At this time it was learned that the patient was, and had been addicted to the use of snuff for the past 35 years, and for the last 8 months owing to fits of mental depression she had been in the habit of keeping snuff under her lip both day and night. The saliva was not expectorated. Twice a week she purchased an 8 oz. jar of snuff. Recently she had taken considerable more whiskey and beer than ever before. Analysis of the snuff showed approximately 0.2% of lead. Lead was also found in the urine and feces of the patient.

The snuff was taken away from her and with rectal feedings and the administration of sedatives the patient improved and soon was able to take a bland diet. During the next few weeks she showed considerable improvement. Then an attempt was made to put her on a low calcium diet with the administration of ammonium chloride. This was discontinued in a short time because of the poor appetite and the mental dissatisfaction. The patient remained in the hospital until the latter part of February showing some improvement in nutrition on a milk diet and symptomatic treatment. Against our advice she left the hospital.

On April 10th the patient was again admitted to the hospital and showed all the manifestation of a long wasting illness. Her husband stated that in spite of all precaution the patient had gotten hold of snuff and had been taking it as before and with the taking of snuff, her appetite failed and nausea and vomiting had again set in. There were no significant changes in the physical signs except those related to the mental and nervous systems, with the exception of a moderately severe cystitis. The neurological examination made at that time follows in full:

The patient lies partially on back and side with head moderately flexed on thorax, back partially arched, with legs drawn up. The attitude and expression are constantly changing. For a moment the facies are anxious and staring and the patient is restless, then she becomes more quiet and the facies apathetic and vacant. When the patient cries the upper lip is drawn peculiarly

toward the nose giving a hysterical appearance. The mood of the patient seems to be changing constantly. It is difficult to hold the patient's attention for even a very short time. Intelligence and orientation fair. Memory for recent events is poor. Periods of drowsiness alternate with periods of restlessness. The patient dreams much, particularly pertaining to her family relationship; she states that she has visions while she is "half-awake" of angels coming after her; she says her mother (long dead) talks to her almost constantly. The speech is drawling, articulation is fair.

All the cranial nerves are normal except for diminished sense of smell and taste. Fundi normal.

Motor System: Some atrophy and moderate flaccidity of all muscles of forearm and carpae interossei. Motor power is markedly decreased, particularly on right arm and hand; there is no evidence of paralysis in the upper extremities, the change is principally a weakness or loss of power, or strength. There is present a fair amount of ataxia in the arms; lower extremities are too weak and painful to permit performance of tests, though there is apparently a lower motor neuron paralysis of both lower extremities with contractures of the muscles in flexion.

Reflexes: The deep tendon reflexes of jaw, elbow and forearm are present and slightly diminished. Those of lower extremities can not be elicited because of pain.

The superficial of corneal and pharyngeal reflexes are normal. Those of abdomen not present. There is vesical and rectal incontinence. The skin suggests atrophic changes. There is pitting edema of the feet.

Sensory System: Hyperesthesia over soles of feet. Diminished sensation of pain and touch in both forearms. Disturbed sensation of pain and touch in both legs to knees. Hyperesthesia of palms. Disturbed appreciation of hot and cold below 5th rib. (This is inconstant.)

The patient continued to grow constantly worse and finally developed hypostatic pneumonia and died, July 4th, 1928.

The Clinical Diagnosis was:

Plumbism.

Posterior Root Radiculitis.
Myositis.
Hypostatic Pneumonia.
Aortitis.
Chronic Interstitial Nephritis.
Cystitis.
Atrophy of the organs of reproduction.

Autopsy Report

Drs. P. Brindley and C. B. Sanders.

The body is that of an elderly white woman about fifty years of age. The body is embalmed and rigor mortis is present. The pupils are dilated and equal. There is sordes about the mouth and the gums show a bluish stain along their margins about the teeth.

There is marked emaciation of the entire body especially of the legs and arms. There are contractures of the legs and arms and they cannot be straightened out. There is rather marked edema of the feet and legs so that they pit on pressure. There are bed sores over the buttocks. On the anterior abdominal wall to the right of the mid-line and extending up from the umbilicus there is a scar about 15 cm. long. Dense fibrous adhesions are present between the under surface of the liver and the transverse colon. There is absence of the gall bladder and appendix. Rather dense fibrous adhesions between the capsule of the liver and the surrounding structures.

Heart: Gross: Weight 200 grams. The right side shows a slight amount of dilatation. All of the chambers are filled with post mortem clots. The mitral and aortic valves show a slight thickening of their margins. There are several raised yellowish patches in the first part of the aorta. Microscopic: some of the muscle fibers appear

larger than normal and show large nuclei, but many of the fibers are of normal size or smaller than normal. There is apparently a slight increase over the normal of the golden yellow pigment found at the poles of the nuclei. A slight overgrowth of connective tissue is present.

Lungs: There are a few petechial and ecchymotic hemorrhages beneath the pleura of the left lung. The posterior portion is of a dark red color and on cut section shows an excess of blood tinged fluid. There are several areas in the lung which show a decrease in crepitus. The right lung is similar to the left and in addition shows, on cut section, multiple areas of consolidation which stand out above the neighboring cut surface. There are several small greyish nodules in the upper lobe which look like healed tubercles. There is a small dark red wedged-shaped area in the lower margin of the upper lobe. The mediastinal nodes show greyish areas of caseation and also a large amount of coal pigment. Microscopic: the vessels are filled with blood. Some of the bronchi contain many polymorphonuclears and desquamated epithelium. Neighboring alveoli also contain a similar inflammatory exudate while many of the alveoli still further away from the bronchi are partly or completely filled with a serous fluid intermixed with fibrin and red blood cells. A few pigmented cardiac failure cells are present. The mediastinal nodes contain black granules of pigment, apparently coal pigment. There is also a definitely walled off partially healed conglomerate tubercle.

Spleen: Gross: weight 338 grams. On section there is an excess of blood and fibrous tissue. The pulp is soft and can easily be scraped away by the knife. Microscopic: there is a rather marked excess of blood. The pulp is increased in amount and there is a marked amount of yellowish brown pigment both within the phagocytic cells and between them. The central splenic arteries are thickened and fibrosed with hyalinization of the fibrous tissue. There is fibrous tissue over-growth with hyalinization in the trabeculae.

Liver: Gross: weight 1,700 grams. The liver has rounded edges. On cut section, there is an excess of blood and the liver has a mottled nutmeg appearance. Microscopic: in scattered areas the liver cells show a fatty infiltration.

Kidneys: Gross: weight 200 grams. The capsule strips with difficulty leaving a roughly and finely granular surface with several subcortical cysts present which are about 10 mm. in diameter. On cut section there is a slight thinning of the cortex. The right kidney is similar to the left. Weight 200 grams. Microscopic: the vessels are distended with blood. Some of the glomeruli show enlargement. Congestion of the glomerular vessels, and swelling of the endothelial cells. The tubules, especially the loops of Heule and collecting tubules, show degeneration, desquamation and some necrosis. Some increase in interstitial tissue is seen especially in the cortex. Adrenals: show nothing unusual.

Pancreas: Gross: shows nothing unusual. Microscopic: there is an increase in fibrous tissue in the walls

of the ducts. The vessels are distended with blood.

Genito-Urinary System: Gross: the bladder contains about 50 cc. of a turbid urine. The mucosa is congested and shows many petechial and ecchymotic hemorrhages. There is a deposit of a muco-purulent exudate on the mucous membrane.

The Uterus: Gross: is smaller than normal and the walls are atrophic and fibrosed. The ovaries are small and fibrotic. Microscopic: the uterine muscle is atrophied and there is an increase in fibrous connective tissue. The glands are atrophic. There are many lymphocytes in the endometrium and a less number in the myometrium.

Gastro-Intestinal System: Gross: the stomach contains a small amount of mucus and food. There are many petechial and ecchymotic hemorrhages in the mucosa. The rectum contains dark black fecal material. There are some petechial and ecchymotic hemorrhages in the mucosa of the colon and small intestine. An excessive amount of mucus is present in the color. There are also a few small ulcers in the colon. Microscopic: small hemorrhages are seen in the mucosa, and in areas we find absence of superficial portions of mucous membrane.

Central Nervous System:* Gross: the brain and cord show nothing unusual grossly. Microscopic: different sections of central nervous tissue, posterior root ganglia and periphereal nerves were stained with Harris' hematorylin and phloxine; Heidenhain's iron hematoxylin; and Weigert's myelin sheath stain.

The brain showed nothing unusual.

The spinal cord showed many of the anterior horn cells atrophied and degenerated with a faint yellowish rather diffuse pigmentation that in some instances completely replaces the faded nucleus. Certain ganglion cells in the nucleus dorsalis showed slight evidence of degeneration. The posterior root ganglion cells contained a large amount of yellowish brown definitely granular pigment arranged perinuclearly. The ganglion cells otherwise stained well.

The periphereal nerves showed nothing unusual.

Anatomical Diagnosis: Atheroma of the aorta; Chronic mitral and aortic valvulitis; Chronic fibrous pleurisy; Hypostatic congestion and pneumonia; Hypostatic congestion; Tuberculous lymphadenitis; Chronic interstitial splenitis; Chronic glomerulo-nephritis; Atrophy of the uterus, tubes and ovaries; Petechial and ecchymotic hemorrhages of mucous and serous membranes; Hemorrhagic cystitis; Surgical absence of the gall bladder and appendix.

Microscopic Diagnosis:

Heart: slight hypertrophy, with beginning later atrophy.

Lungs: hypostatic, lobular pneumonia, tuberculosis of hilus nodes. Anthracotic pigmentation of nodes.

Spleen: congestion, increased pigment, with a slight chronic interstitial splenitis.

Liver: fatty infiltration, slight.

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Editorial

Dessicated Stomach in the Treatment of Pernicious Anemia

Following Castle's demonstration that the stomach of normal individuals secreted a substance which could develop a blood-maturing principle from meat, Sturgis, Isaacs and Sharp began experiments to determine the nature of the material in the stomach which could produce a hematopoietically active substance. Sharp, on the basis of an original theory, decided that the feeding of stomach should have the same effect on patients with pernicious anemia as liver. A preparation was made by dessicating fresh whole hog stomach and defatting with petroleum benzine, so that 30 gm. of the final material represented 218 gm. of the fresh tissue. This preparation has very little odor, and practically no taste. Daily feedings of from 15 to 30 gm. of this preparation in suspension in water were given to three consecutive patients with typical pernicious anemia. One of these patients, a man, aged 57 years, had been treated with a preparation of liver extract about two years previously, receiving about 6 vials daily, representing the extract from 600 gm. of fresh liver. At that time his initial red blood cell count varied between 800,000 and 1,000,000 per cubic millimeter, and his maximum reticulocyte count was 16 per cent on the tenth day of treatment. He developed a complete remission, but later had a complete relapse after discontinuing the treatment. With an initial red cell count of 1,200,000 per cubic millimeter and a hemoglobin of 29 per cent, he was placed on 30 gm. of dried hog's stomach, with a resultant maximum rise of 18.8 per cent of reticulocytes on the seventh day. He was fed 30 gm. daily of dessicated whole stomach from the first to the twentieth day; from then on he was given 15 gm. of the substance daily. No hydrochloric acid was given. Daily counts of the reticulocytes after the twenty-fourth day showed a variation of from 0.1 to 1.1 per cent. On the forty-sixth day the red blood cell count had risen to 4,430,000 per cubic millimeter, the hemoglobin to 76 per cent. The white blood cells had risen from 2,400 to 5,400 per cubic millimeter; and the patient showed a marked subjective and objective improvement, which began early in the course of the treatment. The second patient was under observation for fourteen days only. Given the same treatment of 30 gm. dried hog's stomach daily, at the end of twelve days, his red cell count and hemoglobin had risen, the patient felt greatly improved and left the hospital. The third case was a man, age 26 years, with an initial red blood cell count of 1,470,000 per cubic millimeter, a white blood cell count of 7,500 and a hemoglobin of 35 per cent, who was given 30 gm. daily of the dried stom-

ach which had been defatted with petroleum benzin. In addition the patient received 4 cc. of dilute hydrochloric acid in 250 cc. of water with each meal, but this was not taken at the same hours that the dessicated stomach was given. There was a very rapid and remarkable improvement similar to that observed in patients with pernicious anemia following the use of liver. In nineteen days the red blood cell count rose to 3,240,000 per cubic millimeter, the white blood cells were 4,300 per cubic millimeter, and the hemoglobin 60 per cent. In all three of these cases no liver or liver extract had been given for two months or longer before the treatment with dried stomach had begun. From the well known occurrence of spontaneous complete remissions in the course of pernicious anemia, with return of blood to normal condition and the conversion of a megaloblastic marrow into a normocytic marrow, these cases are all too insufficient evidence upon which to base as yet unqualified statements as to the value of dessicated stomach feeding, and as to whether it will replace the use of liver and liver extract. This new treatment must be tried out on a sufficiently large number of cases in order to exclude the possibility of spontaneous absolute remissions so characteristic of pernicious anemia. Should it be proved by further investigations that the remissions are not spontaneous, but are due to the use of dessicated hog's stomach, a great advance in the treatment of pernicious anemia will have been made. Tasteless and practically odorless, the new preparation will have a great advantage over the use of liver and liver extract, and the treatment should be much less expensive than that with liver. Hogs' stomachs are, we believe, of not much commercial value at the present time, representing practically waste material. The process of dessication and defatting will add but little to the cost of the preparation, so it is to be hoped that further investigation as to the remission-provoking power of the dried hog's stomach product will be as successful as these three preliminary observations promise it to be. If the hog's stomach be shown to contain an active hematopoietic substance, as apparently do liver and kidney, it is interesting to speculate with the idea that pernicious anemia patients have lost, or have never had, the ability to secrete within their stomachs a substance which has the power to produce a blood-maturing material from food. The question also arises as to what other tissues may contain the same principle. If the hog's stomach, why not the hog's intestine?

Eleventh Decennial Pharmacopoeial Convention

This Convention for the revision of the Pharmacopoeia of the United States has been called for May 13, 1930 in Washington, D. C. All delegates must register at least sixty days before the Convention, the latest date for such registration being set at March 14, 1930. As is always the case when the time for a new Pharmacopoeia approaches there is more or less discussion as to the extent of the present day use of deleted pharmacopoeia drugs. A number of efforts have been made in the past to secure exact facts upon which to base

correct judgments for the U. S. P. Scope, and the Committee on Revision is again issuing an appeal for help in making such a study. To accomplish this end they have issued a questionnaire, which has been suggested by various physicians of the Committee, as a check upon the decisions of the past twenty years as to what products which were official in the Eighth or Ninth Revisions, but were not admitted to the U. S. P. X., are in professional demand, and what is the extent of this demand. Physicians and pharmacists are earnestly invited to coöperate in this survey. There follows a long list of the medicinal products which were official in the Eighth and Ninth Revisions but were omitted from the Tenth. Physicians are asked to mark "O," indicating "Often," "R" indicating "Rarely" or "N" meaning "Never," after each of the items listed, to indicate the personal use of the item in their practice. Pharmacists are first asked the number of times the products listed have been ordered on the last 300 prescriptions they have filled. While 300 prescriptions are mentioned as the minimum number to examine, it is urged, that whenever possible, this number be increased to 500 or 1000, or even more. But the number examined must be clearly indicated, and these must be in sequence, filed, and must be of the current year, 1929. Secondly, pharmacists are asked to indicate if any of these items have been called for over the counter by laymen, during the year, 1929, and, if possible, how often. There is also space for additions, in which the physician is asked to insert the titles of such therapeutic agents of the "newer materia medica" that he would recommend for inclusion in the next Pharmacopoeia. Copies of this questionnaire will be sent to any one who is interested on addressing E. Fullerton Cook, Chairman of Revision, United States Pharmacopoeia, Tenth, 636 South Franklin Square, Philadelphia. These questionnaires are to be returned before December 31st, 1929. It is desirable that physicians interested in the revision of the Pharmacopoeia should assist the Committee in furnishing such facts as are above requested.

Abstracts

Death During Remission Stage of Pernicious Anemia. By I. ZADEK (Klin. Wochenschrift, August 13, 1929, p. 1527).

That pernicious anemia is a chronic disease characterized by striking spontaneous remissions and recidives has long been recognized. During such remissions it has been frequently observed that the blood picture may return to normal or approximately so; the hyperchromatic megalocytosis characteristic of the disease may disappear wholly. Since the introduction of the liver-treatment such periods of improvement occur much more frequently than in the past, during which the hematologic examination shows none of the blood changes characteristic of pernicious anemia. When a patient is examined during such a stage of remission the diagnosis of pernicious anemia by means of the blood examination is not possible. Only the presence of the accompanying clinical symptoms of achylia gastrica, funicular myelitis, myocardial degeneration and glossitis, which are not affected by the liver-treatment, will lead to the suspicion of a remission-stage of the disease. The occurrence of spontaneous absolute remission stages of pernicious anemia without characteristic hyperchromatic myelocytosis was emphasized by Zadek before the discovery of the liver treatment. The brilliant results of the new therapy have fully confirmed his views as to the assumption that pernicious anemia is not a primary disease of the bone-marrow. Zadek long before the liver treatment of the disease had demonstrated the occurrence of a metaplasia of the megaloblastic bone-marrow of the fully-blown and recidive stages of the disease to the fatty marrow of the remission stages by the direct examination of marrow removed from the living patient. The earlier views assumed a megaloblastic or megalocytic regeneration for the period of remission, and a persistence of megaloblastic marrow in this period. The normocytic blood-formation of the remission period must lead to a denial of this view, for it stands to reason that an orthochromatic, normocytic blood-picture, without macrocytic or megalocytic hyperchromia, without increased vital staining, and with physiologic blood-volume index must indicate a physiologic condition on the part of the blood-forming tissues. In confirmation of his views concerning the normal state of the bone-marrow during the remission period, Zadek reports the study of two cases dying during the remission period, one without liver treatment and one with it. In the bone-marrow of the first case megaloblasts were completely lacking, and normoblasts were abundant, with many erythrocytes and nests of granulocytes between the fat-areas. Megakaryocytes were present. In the second case the marrow showed abundance of erythrocytes without megalocytes, and numerous erythroblasts, predominately in the form of small normoblasts with small clumped thick nuclei. Between these there were nests of granulocytes with a striking abundance of eosinophile myelocytes, but only occasional myeloblasts. Megaloblasts were wholly absent. It is of especial interest to note that the sternal marrow of this second patient had been examined during life during the full-blown stage of the disease and that it then showed erythrocytes with slight anisocytosis and rich polychromasia, megalocytes, normoblasts, and transitional forms to macroblasts and megaloblasts. Death occurred from influenza after a year on liver diet with complete remission. Marrow taken from the sternum at the point of original puncture was cytologically wholly different from that first examined. It is interesting to note that in both of these cases dying during a remission stage of pernicious anemia the specific megaloblastic character of the bone-marrow should be wholly absent. In the case that had been treated with liver the increase in eosinophile myelocytes in the

bone-marrow corresponded to the frequently observed eosinophilia of the remissions due to liver treatment. Since it may be assumed that cases of death through intercurrent diseases during absolute remission periods of pernicious anemia due to liver treatment will more frequently come to autopsy, it is highly desirable that they be studied for further information as to the nature of the remission and of the relationship between hemolysis and regeneration. Zadek believes that it is highly desirable that a thorough microscopic analysis of the organ changes (anadenia ventriculi, funicular myelitis, papillitis and atrophia linguae, haemosiderosis hepatis, myo-degeneratio cordis, etc.) accompanying the full-blown stage and the recidives should be carried out in the stage of absolute remission for the determination of a possible improvement of these conditions through the liver diet. It would be of great interest to determine through exact investigations whether, and to what extent, the individual organic complications of pernicious anemia are reversible in the period of absolute remission.

Constitutional Infantile (Pernicious-like) Anemia. By E. Uehlinger (Klin. Wochenschr., August 6, 1929).

The author reports a case of infantile, constitutional anemia, pernicious in character, occurring in a boy of 6 years. The cause of the anemia was regarded as the result of a quantitative underdevelopment of the red bone-marrow, without change of bony structure. The blood-forming marrow present was completely capable of functioning, but its total mass was greatly reduced. This red blood cell-forming marrow was limited to the shaft and upper diaphysis of the femur, and to small islands in the vertebrae. All other marrow spaces were filled with fatty tissue only (lipomatosis ex vacuo). The bony substance was neither increased nor lessened in amount. There was no increase in hemolysis. The result of the hypoplastic marrow is a high grade anemia and leukopenia, and a diminution in the number of blood-platelets. When their number falls below 45,000 hemorrhagic diathesis appears as the first symptom; this intensifies the anemia. The marrow present attempts to cover the loss through regeneration, but because of its small mass is unable to do so. There is an intense post hemorrhagic regeneration, which leads to anisocytosis, poikilocytosis, polychromasia and macrocytosis. The iron set free through blood destruction is made use of in the regeneration, so that the hemosiderosis of the spleen, liver and bone-marrow is very slight. The thrombocyte count falls quickly because of the repeated hemorrhages and insufficient regeneration. The hemorrhagic diathesis becomes more general, and increases to a final fatal hemorrhage. This case presented multiple malformations in various years; absence of left thumb, hypoplasia of left thumb, absence of right kidney, abnormal left kidney, aplasia of right seminal vesicle and right-sided genitalia, rudimentary appendix, incomplete lung lobulation and bristly hair. This multiplicity of malformations speaks for a vitium primae formationis. This disturbance occurred during the period of organ-development, since the single tissues were functionally capable. This form of anemia may be familial. The clinical picture is predominated by the hemorrhages in skin and mucous membranes resulting from the thrombopenia due to the poverty of blood. From pernicious anemia the condition is differentiated by the absence of remissions, megaloblasts and urobilinogenuria, and by the age. Pernicious anemia under 10 years is extremely rare. From splenic anemia it is differentiated by the normal-sized spleen and liver, the leukopenia and the age; from hemophilia by the normal coagulation time; and from hemolytic anemia by the normal spleen, normal resistance of the red blood cells and the lack of increased hemolysis. Both this form of constitutional, infantile anemia and the essential thrombopenia of Frank begin with a hemorrhagic diathesis. In the infantile anemia the bone-marrow damage is not limited to the megakaryocytes, but in the later stages of the disease attacks the whole erythropoietic system, and leads to a marked change in the red cell picture, which may be so marked that megalocytes and megaloblasts may appear. In the case described by Uehlinger the changes in the hypoplastic bone-marrow were limited to those of a marked regen-

erative erythropoiesis with the output into the circulation of anisocytotic and basophile granulocytes. From the differential points given above, it would seem clear that in the infantile, pernicious-like anemia there is a well-defined clinical picture.

Zur Frage der Schutzstoffe bei Syphilis. By A. Hauptmann and A. Gallinek (Klin. Wochenschr., August 6, 1929, page 1485).

Cohn had previously published the results of his work on the occurrence of protective bodies in experimental syphilis, in which he found that a spirocheticidal action of the sera of syphilitic rabbits resulted after the third injection of spirochetes. The sera of human syphilitics in different stages of the disease showed no such effects. On the other hand the serum of paretics, who had been treated with injections of dead spirochetes showed the same effect as the sera of syphilitic rabbits. The work of Hauptmann and Gallinek paralleled that of Cohn only in part, for Cohn worked with experimental syphilis and concluded that immune bodies were found only in that form; Hauptmann and Gallinek found evidence of their formation in human syphilis. These investigators worked with spirochetes derived from the Truffi-rabbit chancre. The phagocytes used were obtained from artificial exudates in the abdominal cavity of rabbits according to the method of Hamburg. The human sera used were only employed in wholly fresh condition, and only the active sera of untreated cases were made use of. The microscope was built into a Nuttal thermostat, so that a constant temperature of 37-38° was maintained. The dark fiield lamp was used for only short periods, in order to avoid temperature changes. Observations were made partly in ringed preparations and partly in hanging drops on liquid paraffin. The movement characteristic of spirochetes appears to be a pendulum movement which in reality is a rotation. In addition to this pendulum effect there occurs the knicking or bending motion. In the middle of the organism there will occur suddenly a knicking; the organism will either immediately straighten out again or will remain knicked for some time. Whether this knicking is, as Oelze assumes, the sign of a beginning disintegration, is regarded as doubtful by Hauptmann and Gallinek, since they observed it to occur very early in spirochetes which were under observation for many hours before movement ceased. They also had very frequently the impression of locomotion of the spirochetes, in contrast to Oelze's view that such a spirochete movement did not occur. This apparent locomotion was the first movement to cease, so that its cessation may be regarded as an expression of least damaged vitality on the part of the organism. Actual phagocytosis of the spirochetes by the phagocytic cells was never observed, although the authors describe many interesting phenomena suggesting its occurrence. No evidence of agglutination was seen. The lowering of vitality showed itself first in the cessation of locomotion, then the pendulum motion became weaker, and finally ceased. The spirochetes then presented a stiffened appearance and finally they fragmented into a droplet-like row. Expressed in different grades of strength of vitality, the first grade would be that characterized by locomotion, strong pendulum movement, the knicking motion, and the affinity for the cells (as shown by anchoring, tangential position, star-formation and bridging between two cells). The second degree would be shown by a moderate pendulum movement as the only form of motion shown by the organism; while the third degree of vitality would be the loss of pendulum motion and beginning stiffening. Finally, the fourth stage would show itself in complete stiffening and fragmentation, which would represent its complete death. Their experiments were carried out in ten series in which the action of normal sera, with and without phagocytes, was compared with that of luetic and metaluetic sera, with and without the addition of phagocytes, on spirochetes of the same sourse or origin, on the same day and under the same conditions. Ten normal cases, ten secondary syphilitics, eleven cases of paresis and two cases of cerebrospinal lues were so studied. In all cases, except in the two of cerebrospinal lues the spirochetes employed were obtained from the Truffi-rabbit chancre. In all of these expe-

riments no difference was observed in the action of the serum as far as the presence or absence of phagocytes was concerned. In most of the normal sera the degeneration phenomena on the part of the spirochetes began after three hours, and were completed after five hours. In half of the secondary-syphilitic sera the beginning of the degenerative phenomena occurred in ten minutes and death of the spirochetes was complete after thirty minutes. In the other half of the sera from secondary syphilitic cases the death-phenomena began after one and a half hours and were completed after one and a half to two hours. Only in one case was the two hour period observed. Investigation of this case, which has been believed to have been untreated, showed that the patient before entering the clinic had already had 2 gm. of neosalvarsan and numerous bismuth injections. The sera from the cases of paretics behaved in the same manner as the normal sera. In the two cases of cerebral syphilis, the appearance of death-phenomena took place extremely quickly. In these two cases the spirochetes used were taken from a culture. Only in these two sera was any difference shown between the phagocyte-containing and the phagocyte-free sera. In the latter the spirochetes remained unaltered essentially longer than in the sera containing phagocytes. It would appear from this that the spirochetes obtained from culture were more susceptible to cell action than those obtained from the animal body. Hauptmann and Gallinek's investigations, therefore, agree with those of Cohn, in that the sera of normal cases and of paretics contain no immune bodies. This confirms the view of Hauptmann as to the immunity-weakness of the paretic organism. On the other hand the work of Cohn which shows that paretics treated with killed cultures of spirochetes produce immune-bodies would seem to contradict Hauptmann's views, but the latter does not find anything in Cohn's result to contradict his view of an insufficient defence on the part of the metaluetic organism, instead of an immunity-weakness, which is more of a constitutional conception, but which can also take place, in that a less virulent spirochete race may excite in an organism capable of defence, a less active defence response. In effect this amounts to the same thing as when a constitutionally defence-weak organism cannot produce sufficient defence against a highly virulent spirochete race. Hauptmann's theory of a less virulent spirochete race as the cause of metalues is only a modern expression of the old theory of "lues nervosa." If the Cohn finding of the formation of immune-bodies in paretics treated with cultures of spirochetes and the absence of such bodies in untreated cases be confirmed, the "insufficient defence" of the metaluetic in Hauptmann's theory may be taken to mean an insufficient stimulation on the part of the weakly virulent spirochete race. Before this question can be wholly decided, further investigations must be carried out to show whether the cultures of spirochetes used by Cohn are more virulent when inoculated into rabbits than are spirochetes cultivated from animals; and, further, whether the immune-body production towards these culture spirochetes is stronger in secondary syphilitics than in paretics. If this be the case, Hauptmann's conception of the constitutional weakness in defence of the paretic is confirmed. All defence on the part of the paretic organism is not wanting, it is present in part, as the occasional presence of gummatous formations in the paretic brain shows, and the occurrence of skin manifestations in the secondary stage of the paretic. If the work of Hauptmann and Gallinek be confirmed that the secondary syphilitic and the brain syphilitic in the secondary stage produce immune-bodies, while paretics do not produce such, it must be granted that one of the essential components of paralysis is a defective defence. Whether this defective defence is a constitutional weakness or whether an insufficient stimulation of a weakly virulent spirochete is the cause must be left for future investigations to determine. In conclusion, there are present in the serum of secondary syphilitics and tertiary brain syphilitics immune-bodies; in paretics none are present in the serum, or, if present, only in small amounts, as in the serum of normal cases. In paresis this insufficient defence on the part of the organism plays an important rôle; whether due to constitution or to a weakly virulent organism remains to be decided.

Reviews

Tularemia. History, Pathology, Diagnosis and Treatment. By WALTER M. SIMPSON, M.S., M.D., F.A.C.P., Director of the Diagnostic Laboratories, Miami Valley Hospital, Dayton, Ohio; Formerly Senior Instructor in Pathology, University of Michigan. Foreword by EDWARD FRANCIS, Surgeon, United States Public Health Service. 178 pages, 53 text illustrations and 2 colored plates. With complete bibliography. Paul B. Hoeber, Inc., New York, 1929. Price in cloth, $5.00.

This book is fortunate in appearing at the psychologic moment. Regarded as a rare disease in 1924, during the last five years, Tularemia has been shown to have a world-wide distribution, and to be of such frequent occurence in man as to assume a position of distinct clinical importance. The history of this disease has been spectacular in the extreme. From its discovery in a California ground squirrel by McCoy, in 1910, up to the present time over 800 cases have been reported in the District of Columbia and in every state of the Union, with the exception of New England, Delaware and Washington; and over 1000 cases have recently been observed in man in Russia, and a smaller number of cases in Japan. It has been shown to be widely distributed in nature in a great variety of animal hosts, occurring chiefly in an infectious bacteriemia of rodents due to the *Bacterium tularense*, particularly in wild rabbits, from which it is commonly transmitted to man through direct contact with the tissue or body fluids of the infected animal, or through indirect transmission from animal to man by means of certain ticks or flies. Besides the wild rabbit the infection has been found to exist in nature among sheep, muskrats, opossums, water rats, ground squirrels, wild mice, wood-chucks, ruffled grouse, and quail. In man the infection has been frequently confused with influenza, typhoid fever and streptococcus infections. There has been a mortality of nearly 4 per cent; in other cases there has been a very slow convalescence with the development of chronic suppurative or granulomatous lesions, associated frequently with marked prostration and debility. The incubation period varies from one day to one week. The onset is sudden, frequently grippe-like in character. Four distinct clinical types exist, the ulceroglandular, the oculoglandular, the glandular, and the the typhoid type. The prolonged convalescence is one of the most serious features of the disease. The microscopic picture of the primary lesion is that of a subacute infective granuloma. The lesions are found chiefly in the regional lymphnodes, spleen, liver and lungs. Foci of caseous necrosis occur in these organs with peripheral epithelioid and fibroblastic proliferations. Because of the histologic similarity in the lesions of tularemia and tuberculosis there is danger in confusing the lesions. Pathologically the lesions of tularemia are to be classed with the infective granulomas. One of the remarkable features of the disease has been its frequent occurrence among laboratory workers. The diagnosis of tularemia can be easily made by an agglutination test, and there should be no excuse in the future for failure to recognize this disease. Dr. Simpson's part in the history of tularemia has also been as spectacular as the rise of the disease from comparative obscurity to its present prominence. During a period of one and a half years he discovered 61 cases in and about Dayton, Ohio. Thirty-two of the patients had acquired the disease during the rabbit season of 1927 and 1928; the remainder had suffered from unrecognized tularemia at osme time during the previous twenty years. It was his Dayton experience that forms the foundation matter of the present book, which is abundantly il-

lustrated by material taken from this experience. The whole story of tularemia from its beginning to the present time is clearly and concisely told in this book. While based primarily upon his personal experience, the book includes an excellent summary of all our present knowledge upon the subject, brought fully up to date, and including a full bibliography of the subject. This work will undoubtedly become a classic upon the subject. First in the field, it achieves merit for its completeness and logical arrangement, conciseness of treatment, with all of the important facts included, and nothing omitted. The book is printed in the usual excellent manner by Hoeber; and the illustrations are similarly well done. It is a necessary book for the library of the up-to-date physician.

Rickets, Including Osteomalacia and Tetany. By Alfred F. Hess, M.D., Clinical Professor of Pediatrics, University and Bellevue Medical College, New York City. 485 pages, 52 illustrations. Lea and Febiger, Philadelphia, 1929. Price in cloth, $5.50.

The publication of a new book on rickets is justified by the fact that since 1918 a new era has been created—that of the Newer Rickets, which has made many time-honored theories in the textbooks no longer tenable. Two discoveries have contributed to the birth of this Newer Rickets, neither of which has depended in any way upon the other. The first came from the biologic laboratory, and consisted of a method of inducing rickets experimentally in animals, rendering it possible to study various aspects under conditions which are subject to exact control and modification. This technique made it possible for the first time to gauge the comparative etiologic importance of faulty hygiene and diet. The second factor, closely following the first, was the discovery that the lack of ultra-violet light or energy plays the dominant rôle in the causation of rickets, and that it is a specific agent for prophylaxis and cure. From the date of these discoveries rickets has been the object of intense investigation in many medical clinics and experimental laboratories. Interest in the disease was further stimulated by the discovery almost five years ago that the ultra-violet rays can also exert their remarkable action indirectly—that they can endow certain oils and foods with antirachitic properties. Lastly it has been shown that a particular sterol-ergosterol could be activated to a remarkable degree. This knowledge not only made available new methods of therapy, but necessitated a revision of our conception of the chemical action of these rays. For twelve years Hess and his numerous coworkers have been almost continuously engaged in investigations relating to rickets. The results of this work have been published in a large number of contributions to various periodicals. The more significant features of the work of these years have been reappraised and incorporated in the present volume. The book, begun about five years ago, has been written for the practitioner as well as for the nutrition worker. Throughout the book, results obtained experimentally in the laboratory have been weighed and appraised in the light of clinical experience. The clinic has been adjudged the final arbiter. A definite attempt has been made to avoid a break with the past, by presenting an unbroken exposition of both eras, welding them together into a homogeneous unit. To this end a short historical review has been introduced at the beginning of almost every chapter. No attempt at a complete bibliography has been made. The aim has been rather to have the bibliography selective and comprehensive. It is arranged according to chapters at the end of the book. In order to present a more complete picture, chapters on late rickets, osteomalacia and tetany have been included. Our point of view regarding these disorders has also been enlarged and clarified during the past decade. The conception of late rickets has been extended by the experiences of Germany and Austria during the post-war period, as well as by the recognition of renal and of coeliac rickets. The new technique used in elucidating rickets has also recently been applied to osteomalacia, and for the first time an opportunity has been furnished of comparing the radiographic appearances, the chemical analysis of the blood and the response to spe-

cific therapy of these two closely related disorders. During the past five years infantile tetany has also been studied intensively from the standpoint of the acid-base equilibrium, and has been rendered much more amenable to treatment through the introduction of the use of acid therapy, as well as of ultra-violet light. While realizing that our knowledge of rickets is far from complete, and that new and important aspects may be discovered in the not far distant future, particularly with regard to pathogenesis, the author considers that so much has been accomplished during the past decade, with a resultant remarkable change in our clinical and scientific points of view that the time for publication seemed fitting. The book consists of a most excellent survey of all the information available upon rickets at the present time. The historical survey of the subject is well written and of great interest. Most important of all is the full discussion of the work of the last decade on rickets and allied conditions from the new standpoints of diet and ultra-violet irradiation. This resumé of the "newer rickets" makes the book of great value to the internist and worker in nutrition. The information contained in it has become a necessary part of the medical education of the present day, and the book a necessary item in the practitioner's library.

Diseases of the Thyroid Gland. By ARTHUR E. HERTZLER, M.D., Surgeon to the Halstead Hospital. With a Chapter on Hospital Management of Goiter Patients by VICTOR E. CHESKY, M.D., Associate Surgeon to Halstead Hospital. Second Edition, Entirely Rewritten. 286 pages, 159 illustrations. C. V. Mosby Company, St. Louis, Mo., 1929. Price in cloth, $7.50.

This new edition presents the results of a continuation of the studies contained in the previous one. The conclusions presented have been arrived at only after a constant comparison of the clinical picture, the pathology and a repeated examination of the patient in after years. The work is based upon individual experience and opinion in an isolated hospital "untrammeled by the opinion of others." The contents are divided into the following chapters: Etiology of goiter; normal morphology; pathologic anatomy; symptomatology of diseases of the thyroid gland; diagnosis of diseases of the thyroid gland; goiters in unusual places; hospital management of goiter patients; topographic anatomy of the thyroid gland; and the technique of operations on the thyroid gland. This book presents a very superficial discussion of the etiology and pathology of goiter. The author apparently has no idea of the theory of a Graves' constitution, or of the relation of a persistent thymus to the so-called toxic forms of goiter. Nor does he evaluate the significance of the constant presence in exophthalmic goiter and the so-called toxic adenoma of hyperplastic lymph follicles with germinal centers. The book contains far too much evidence of having been written "untrammeled by the opinion of others." The illustrations are in part fair, and in part poor. The surgical sections have more practical value than the pathologic.

Diagnostic Methods and Interpretations in Internal Medicine. By SAMUEL A. LOEWENBERG, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, Jefferson Medical College; Assistant Physician to the Jefferson Hospital; Visiting Physician to the Philadelphia General Hospital; etc. 1032 pages, 547 illustrations, some in colors. F. A. Davis Company, Philadelphia, 1929. Price in cloth, $10.00.

The author has ventured to compile a textbook of general information upon medical diagnosis from the standpoint of the rapidly disappearing general practitioner. The book aims to cover the field of diagnostics in internal medicine. It gives instructions on the various methods of examining the patient, descriptions of normal findings, enumeration of pathologic conditions with the normal and pathologic physical signs, and, whenever possible, the reasons for such signs. The signs and interpretations are discussed from the viewpoints of the medical student, the general practitioner and the specialist. The respiratory and cardiac systems are discussed fully and minutely; to the digestive system, the nervous system and urology, adequate space is devoted, while to the skin, nose, ears, eyes, bones

and joints, radiography, the blood, the ductless glands, etc., less space is given, only so much has been allotted as is deemed necessary for the purpose of a general examination. The chapter on laboratory interpretations is limited, in the main, to the interpretation of laboratory analyses by the pathologist, chemist, serologist or clinical laboratory specialist, while only the simplest technical methods are described. There are general chapters on the life insurance examination, industrial examinations and the detection of malingering. The illustrations are of three types: actual photographs of methods of examination and of patients suffering with the particular disease described in the text; drawings calculated to emphasize the descriptions of certain conditions; and photographs of pathological specimens to aid the memorizing of the respective clinical descriptions. This book contains an immense amount of useful information. Its arrangement is good, and the material is concisely expressed. It is illustrated by a large number of pictures well adapted for showing the given condition, but which unfortunately suffer from the rather indistinct reproductions. Glazed paper has been used for the reproduction of the radiographs, and there are very much better than the illustrations given in the text. On the whole, this volume will be of service to the student of diagnosis.

College News Notes

1930 CLINICAL SESSION TO BE HELD IN MINNEAPOLIS

The 1930 Annual Clinical Session of the American College of Physicians will be held in Minneapolis, Minnesota, during the week of February 10, 1930. Dr. S. Max White, 1009 Nicollet Avenue, Minneapolis, is the local General Chairman of Arrangements, and is busily engaged in the preparation of the program. The University of Minnesota Medical School and local hospitals throughout Minneapolis are coöperating in placing their laboratories and clinical facilities at the disposal of the College. The afternoon and evening scientific sessions will be held in the public Auditorium, where also will be housed the Registration Headquarters, Exhibits, etc. The Curtis Hotel, located two squares from the Auditorium, will be headquarters for the Officers, Board of Regents and Board of Governors. Ideal facilities for the Session, the hospitality of the City of Minneapolis and the enthusiasm and earnestness of those making preparations for the meeting combine to assure a most interesting and successful Clinical Session for the coming winter.

PAPERS DELIVERED BEFORE ANNUAL CLINICAL SESSIONS OF THE COLLEGE

Scientific papers delivered before the Annual Clinical Session of the American College of Physicians become the exclusive property of the College for publication in ANNALS OF INTERNAL MEDICINE. It is very important, not only for sake of the Journal, but also for the members of the College at large, to have a complete published record of all papers delivered at each Clinical Session. The ANNALS is the official vehicle of the College for the publication of all such papers.

1929-30 DIRECTORY OF THE AMERICAN COLLEGE OF PHYSICIANS

During the past summer, the Executive Secretary, Mr. E. R. Loveland, completed the publication of a new and complete Directory of the College, and has distributed a copy to every member of record in good financial standing. Members with waiver of fees due to having passed the age limit may secure a copy on subscription of one dollar, fifty cents.

The new edition of the Directory was printed in accordance with the instructions of the Committee on Directory and the Board of Regents. The contents of this edition have been limited to such important biographical data as space permits in a volume of this size, and has been considered necessary and helpful for reference.

Although great effort was directed toward the elimination of errors, it is possible that some incomplete or imperfect data have appeared. Members are requested to advise the Executive Secretary of such errors in order that later corrections may be made.

VOLUME FILES FOR ANNALS

The Executive Office at 133-135 S. 36th Street, Philadelphia, Pa., maintains a supply of box files specially made and indexed for Volume II of ANNALS OF INTERNAL MEDICINE. Volume II was completed with the June, 1929, Number, and should be preserved in one of these Volume Files. The cost is $1.25, postpaid.

Dr. John H. Musser (Fellow and President) delivered the annual oration in medicine, speaking on "The Normal and the Diseased Heart," at the eighty-eighth anniversary meeting of the State Medical Society of Wisconsin at Madison during the week of September 9.

Dr. J. A. E. Eyster (Fellow), Professor of Physiology at the University of Wisconsin, is author of a new book entitled "The Clinical Aspects of Venous Pressure," recently published by The Macmillan Company of New York City.

Dr. George R. Minot (Fellow), Boston, is Editorial Advisor of The Macmillan Company of New York City in the publication of The Macmillan Medical Monographs. The publications of The Macmillan Company are regularly announced on page 1 of the advertising section of this Journal.

At the recent meeting of the California Medical Association at Coronado Beach, California, Admiral E. R. Stitt (Fellow), Dr. W. S. Thayer (Fellow) and Dr. John H. Musser (Fellow) were three of the six speaker guests at this, the fifty-eighth annual session.

Dr. William A. White (Fellow), Superintendent of St. Elizabeth's Hospital, Washington, D. C., is Chairman of the Board of Managers of the Washington Institute for Mental Hygiene.

Dr. Allen H. Bunce (Fellow), Atlanta, was elected a member of the Board of Trustees of the American Medical Association at its last meeting in Portland.

Dr. E. C. Thrash (Fellow), Atlanta, has been appointed Chairman of the Reference Committee on Constitution and By-Laws of the American Medical Association.

Dr. Cornelius Oliver Bailey (Fellow), Dallas, Texas, has been made a Fellow of the Royal Society of Arts, London. It is said that there are only seventeen American physicians who have been elected to this society.

Dr. David C. Wilson (Fellow), has been appointed Associate Professor of Psychiatry and Neurology at the University of Virginia. Dr. Wilson was formerly on the staff of the Clifton Springs Sanitarium, Clifton Springs, New York.

Dr. Bernard L. Wyatt (Fellow), formerly President and Director of the Desert Sanatorium and Institute of Research, announced the opening of an office in Tucson, Arizona, on October 1. Special attention will be given to arthritis and rheumatoid conditions.

Dr. Donald R. Ferguson (Fellow), Philadelphia, is author of an article which appeared in the August Number of the Hahnemannian Monthly, entitled, "Massive Collapse of the Lung Secondary to Bronchogenic Carcinoma."

Dr. Arthur L. Holland (Fellow), New York; Dr. W. W. Herrick (Fellow), New York; and Dr. George E. Brown (Fellow), Rochester, Minn., were among the guest speakers at the Fifth Annual Clinical Congress of the Connecticut State Medical Society at New Haven during September.

Dr. Harlow Brooks (Fellow), New York, is Chairman of the Second Annual Graduate Fortnight of the New York Academy of Medicine, being held October 7-19. Among Fellows of the College offering papers or lectures are:

Dr. Max Einhorn
Dr. Charles A. McKendree
Dr. Charles F. Tenney
Dr. Joseph Lintz
Dr. Aaron S. Blumgarten

Major Robert D. Harden (Fellow), Medical Corps, U. S. Army, has been appointed a member of the National Board of Medical Examiners, succeeding Col. Joseph F. Siler (Fellow), who has been detailed to the Panama Canal Zone for duty.

The following Fellows of the College have been appointed members of the Board of Public Health Advisers for Illinois by Governor Emmerson: Dr. James H. Hutton, President-Elect of the Chicago Medical Society; Dr. William A. Evans, former Health Commissioner of Chicago.

Dr. William S. Baldwin (Fellow), Lorain, Ohio, was recently elected President of the Lorain County Health Council.

Dr. Rock Sleyster (Fellow), Wauwatosa, Wisconsin, recently addressed the Walsworth County Medical Society on "Nervous and Mental Diseases."

At the meeting of the American College of Radiology, at Portland, Oregon, during July, Dr. Rollin H. Stevens (Fellow), Detroit, was elected President-Elect and Dr. Albert Soiland (Fellow), Los Angeles, was re-elected Executive Secretary.

Dr. Curran Pope (Associate), Louisville, was honored by a testimonial dinner at the Annual Meeting of the American Electrotherapeutic Association at Indianapolis, September 11-13.

Lt. Comdr. Elwood A. Sharp (Fellow) has recently resigned his commission in the U. S. Navy.

Capt. Frank L. Pleadwell (Fellow) has been transferred to the Receiving Ship, New York City.

Lt. Comdr. Eben E. Smith (Fellow) has been assigned to the U. S. S. Saratoga.

Comdr. Lester L. Pratt (Fellow) has been assigned to the Navy Hospital, Washington, D. C.

Dr. Gerald B. Webb (Fellow), Colorado Springs, is the Research Director of the Colorado Foundation for Research in Tuberculosis.

Col. Aaron C. Conaway (Associate), Marshalltown, Iowa, was in command of the three hundred and forty-seventh medical regiment at Fort Snelling, July 5-19.

In addition to acting as Director of the Desert Sanatorium and Institute of Research at Tucson, Arizona, Dr. Allen K. Krause (Fellow) will fill the appointment as Clinical Professor of Medicine at Stanford University, San Francisco.

Dr. William Sydney Thayer (Fellow), Baltimore, received the honorary degree of Doctor of Laws at the commencement of McGill University, Montreal, Canada.

Dr. Carroll M. Pounders (Fellow), Oklahoma City, addressed the Stephens County Medical Society at Marlow, Oklahoma, recently.

Dr. Archibald N. Sinclair (Fellow), Honolulu, Hawaii, was elected Secretary of the Hawaii Territorial Medical Association at its last annual meeting.

Dr. Alfred Stengel (Master), Professor of Medicine at the University of Pennsylvania Medical School, member of the Medical Board of the University's Trustees and Chairman of the Building Committee delivered the principal address at the dedication of the new Martin Maloney Medical Clinic Building of the University of Pennsylvania Hospital in Philadelphia on September 20. The Clinic Building costs approximately one million dollars, and will house the general medical outpatient department of the University Hospital, dispensaries for medical and allied groups, a Hydro-therapy and Psysico-therapy Department, special wards for cases requiring special study and care, the Pepper Laboratory of Clinical Medicine and the John Musser Department of Research Medicine. In addition, the Eldridge R. Johnson Foundation for Research in Medical Physics, provided for by the gift of $800,000 by Mr. Johnson, former President of the Victor Talking Machine Company, will occupy the entire sixth floor. The Cardio-Vascular, Gastro-Intestinal, Thyroid, Metabolic and Diabetic, Asthma, Pulmonary and Biometric Clinics will be located in the new building, and both the Pepper and Musser units will have approved facilities for their work.

Dr. Stengel, it is reported, was directly responsible, through his contacts with Mr. Maloney and Mr. Johnson, for securing the interest of these capitalists and their subsequent gifts to the University of Pennsylvania.

Dr. Emanuel Libman (Fellow), New York, recently donated $10,000 to Johns

Hopkins University Medical School for the establishment of a lectureship in the history of medicine. It is to be named the Hideyo Noguchi Lectureship.

Dr. Walter A. Bastedo (Fellow), New York, was awarded the honorary degree of Doctor of Science at the Columbia University Commencement last June.

Dr. Frank Smithies (Master), Chicago, delivered the opening address of the 1920-30 program of The Academy of Medicine at Rochester, New York, on October 2. Dr. Smithies' subject was "Deficient Liver Function as a Cause of Chronic Skin Lesions."

Dr. W. Blair Stewart (Fellow and Governor for New Jersey) was the representative delegate from the Medical Society of New Jersey to the annual meeting of the Medical Society of Pennsylvania at Erie, Pa., during the early part of October.

Dr. James L. McCartney (Fellow), Hartford, Conn., was appointed Chief of the Division of Mental Hygiene in the Connecticut State Department of Health and began his service August 1. Dr. McCartney was elected a Fellow of the College at the last session. For the last several years he has been specializing in neuro-psychiatry, and last year was with the National Committee for Mental Hygiene in New York City. He is now in charge of the Neuropsychiatric work in the State of Connecticut.

Dr. Robert M. Moore (Fellow), Indianapolis, presented a paper on "Subacute Bacterial Endocarditis—Some Clinical Observations," before the Indiana State Medical Association at Evansville, Indiana, September 26.

Dr. Joseph Kopecky (Fellow), Galveston, is reported to have recently resigned the professorship of Clinical Medicine and Clinical Pathology at the University of Texas School of Medicine to go into private practice at San Antonio. Dr. Kopecky recently returned from Mexico City where he served during the summer as exchange Professor at the Mexico National University Medical School.

Dr. Fred Morris Meixner (Fellow), Peoria, Ill., is the author of an article entitled, "Recognizing Tonsil Infection," appearing in the June, 1929, Issue of the Illinois Medical Journal.

"Physical Standards in Aviation" is the title of another article by Dr. Meixner in the August Issue of the Bulletin of the Peoria Medical Society.

Dr. W. H. Marshall (Fellow), Flint, Michigan, contributed a paper on "Drug Therapy" in a Symposium on Therapeutics given at the meeting of the Michigan State Medical Society, Jackson, Michigan, September 19.

Dr. Antonio D. Young (Fellow), Oklahoma City, was recently elected Chairman of the combined Medical and Neurological section of the Oklahoma State Medical Society.

Dr. Conrad Wesselhoeft (Fellow), Boston, was recently promoted to Assistant Professor of Theory and Practice at Boston University School of Medicine.

Dr. A. B. Olsen (Fellow), Battle Creek, Michigan, is the author of an article, "Some Observations of the Treatment of Surgical Tuberculosis by Heliotherapy," appearing in the September Issue of the Journal of the Michigan State Medical Society. This paper was read before the last annual meeting of that Society, and was illustrated by slides showing the treatment as given by the natural sunshine and artificial light in Switzerland and in England.

At the joint meeting of the American Electrotherapeutic Association and the Western Physical Therapy Association, held at Indianapolis, Indiana, September 11-13, Dr. Olsen read a paper on "Cryoaerotherapy or Cold Air Treatment." The paper was illustrated by slides showing this treatment as given at Leysin, Switzerland, Alton Park,

England, and at the Battle Creek Sanitarium.

Dr. Curran Pope (Associate), Louisville, Kentucky, was honored by a testimonial dinner given by the American Electrotherapeutic Association and the Western Association of Physical Therapy "in recognition of his honorable service of forty years as physician, neurologist, author, editor-writer, teacher, speaker and as one of the real pioneers in the domain of Physical Therapy in Medicine" at the Lincoln Hotel in Indianapolis, Indiana, on September 11.

Dr. V. C. Rowland (Fellow), Cleveland, was recently elected trustee of the Ohio Public Health Association for a term of three years.

Dr. Julius Friedenwald (Fellow), Baltimore, has been elected Chairman of the Gastro-enterological Section of the American Medical Association for the coming year.

Dr. Russell C. Pigford (Associate) has been appointed Head of the Department of Electrocardiography at St. John's Hospital, Tulsa, Oklahoma.

Dr. Pigford presented a paper on "Reliable Signs of Myocardial Disease" at the July meeting of the Osage County (Oklahoma) Medical Society.

Dr. Ada E. Schweitzer (Fellow), Indianapolis, Indiana, supervised the conduct of the "Better Baby Demonstrations" at the Indiana State Fair during the summer. 1,239 babies were examined, and 65,000 visitors who came to see the demonstrations were furnished information concerning child care, feeding and habit training. The attractive manner of presenting health education won much commendation. The American Medical Association donated 2,000 sample copies of Hygeia for distribution at the demonstration nursery. Dr. Schweitzer is the Director of the Division of Infant and Child Hygiene of the Indiana State Board of Health.

Dr. Aaron C. Conaway (Associate), Marshalltown, Iowa, has announced an association with Dr. Aanatole Kolodny, Professor of General Surgery and Neurological Surgeon at the Iowa State University College of Medicine. Dr. Conaway is Councillor for the Fifth District of the Iowa State Medical Society, President of the Marshall County Medical Society and President of the staff of the Deaconess Hospital.

At the meeting of the Dallas Southern Clinical Society, September 18-20, the following members of the American College of Physicians delivered papers:

Dr. Eugene Rosamond (Fellow), Memphis —"Enterospasm."

Dr. Edgar W. Loomis (Associate), Dallas—"Bilateral Phlebitis."

Dr. H. Leslie Moore (Fellow), Dallas—"The Overactive, Undernourished Child."

Dr. J. L. Goforth (Fellow), Dallas—"Immologic Diagnosis, Treatment and Prevention of Disease."

Dr. D. L. DeBuys (Fellow), New Orleans —"Some Interesting Observations in the Newly Born."

Dr. Robert M. Barton (Associate), Dallas—"Classification of Heart Disease."

Dr. C. O. Bailey (Fellow), Dallas—"Treatment of Acute Respiratory Infections with X-Ray."

Dr. Tate Miller (Associate), Dallas—"Modern Management of Gastric Ulcer."

Dr. Porter P. Vinson (Fellow), Rochester, Minn.—"Differentiation and Treatment (with special reference to Bronchoscopic Management) of Chronic Pulmonary Diseases."

Dr. G. E. Brereton (Fellow), of Dallas, is the Treasurer of the above Society.

Dr. G. L. Pinney (Fellow) has been made Chief of Staff of Internal Medicine at the Mary Lanning Memorial Hospital at Hastings, Nebraska.

Dr. Austin B. Jones (Fellow) addressed the Missouri State Medical Association at Springfield, Missouri, May 16, on "Agranulocytic Angina."

Dr. Hubert Work (Fellow), founder of Woodcroft Hospital at Pueblo, has returned to Colorado and has offices with his son Dr. Philip Work, in Denver. Dr. Work has been in Washington for several years, serving as Postmaster General and Secretary of the Interior, and more recently as Chairman of the national Republican Committee. He was a member of the House of Delegates of the American Medical Association for several years and President of the Association in 1921.

Dr. Harold E. Robertson (Fellow), Rochester, Minn., is a speaker on the program of the fifty-ninth annual session of the Colorado State Medical Society, on "Some of the Newer Aspects of Carcinoma"; Dr. Earl H. Bruns (Fellow), Medical Corps, U. S. Army, will speak on "Air Embolism as a Complication in Artificial Pneumothorax Therapy", and Dr. Gerald B. Webb (Fellow), Colorado Springs, will exhibit the Harvey film which was prepared by the Royal College of Physicians of London for the tercentenary of Harvey.

Dr. Carl Vernon Weller (Fellow) published in the Archives of Pathology, March, 1929, the most complete survey of the Pathology of Primary Carcinoma of the Lung that has yet been made.

In the Journal of Cancer Research for October, 1929, he has an article on "Entdifferentiation in Primary Carcinoma of the Bronchi and Lungs."

In the Journal of Cancer Research for July, 1929, Dr. A. S. Warthin (Master) has an article on "Papillary Cystadenoma Lymphomatosum."

In the British Medical Journal for August 10th Dr. Warthin has an article on "Lesions of Latent Syphilis."

The American Journal of Syphilis for July, 1929, contains an article by Dr. Warthin on "A Silver-starch-gelatin Method for the Demonstration of Spirochetes in Single Tissue Sections." This article will be published also in The British Journal of Venereal Diseases.